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(54) **ALTERNATIVE SPLICING VARIANTS OF GENES ASSOCIATED WITH PROSTATE CANCER RISK AND SURVIVAL**

(71) Applicant: **The George Washington University**, Washington, DC (US)

(72) Inventors: **Norman H. Lee**, Dayton, MD (US); **Steven R. Patierno**, Chapel Hill, NC (US); **Bi-Dar Wang**, Potomac, MD (US)

(73) Assignee: **The George Washington University**, Washington, DC (US)

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C12Q 1/68 (2006.01)
C07K 14/47 (2006.01)
C12N 15/113 (2010.01)

(52) **U.S. Cl.**

CPC **C12Q 1/6886** (2013.01); **C07K 14/47** (2013.01); **C07K 14/4748** (2013.01); **C12N 15/1137** (2013.01); **C12Q 2600/118** (2013.01); **C12Q 2600/156** (2013.01)

(58) **Field of Classification Search**

CPC C12N 5/111; C12N 15/113
See application file for complete search history.

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Primary Examiner — Amy Bowman

(74) *Attorney, Agent, or Firm* — Blank Rome, LLP

(57) **ABSTRACT**

Disclosed are novel splicing variants of the genes associated with prostate cancer risk and survival, particularly splicing variants of PIK3CD, FGFR3, TSC2, RASGRP2, ITGA4, MET, NF1 and BAK1. The disclosure also relates risk assessment, detection, diagnosis, or prognosis of prostate cancer. More specifically, this disclosure relates to the detection of certain splicing variants of PIK3CD, FGFR3, TSC2, RASGRP2, ITGA4, MET, NF1 and BAK1.

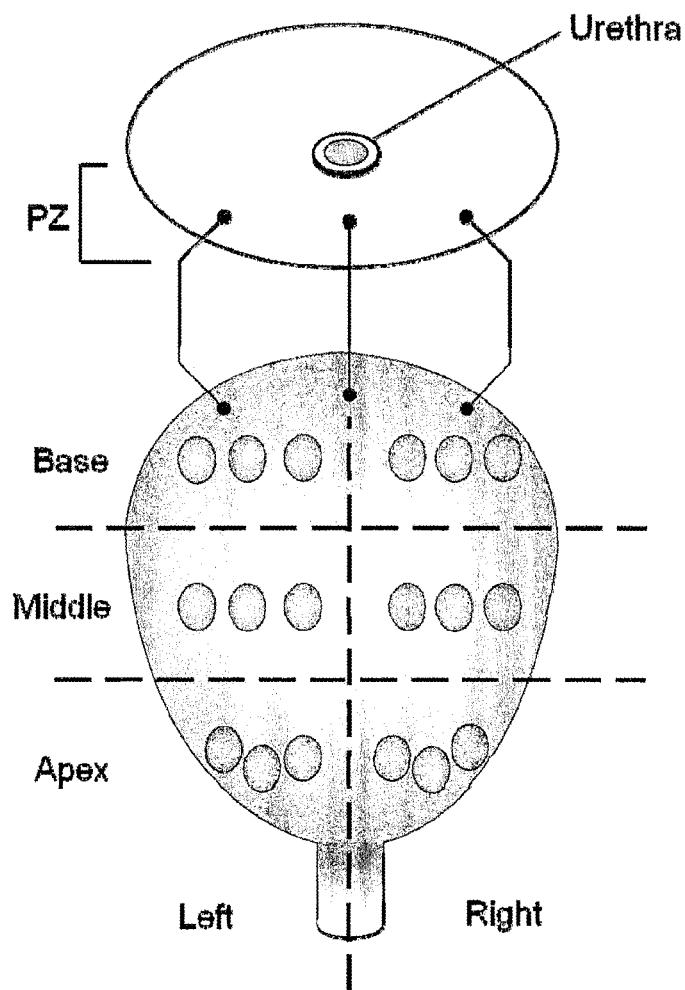
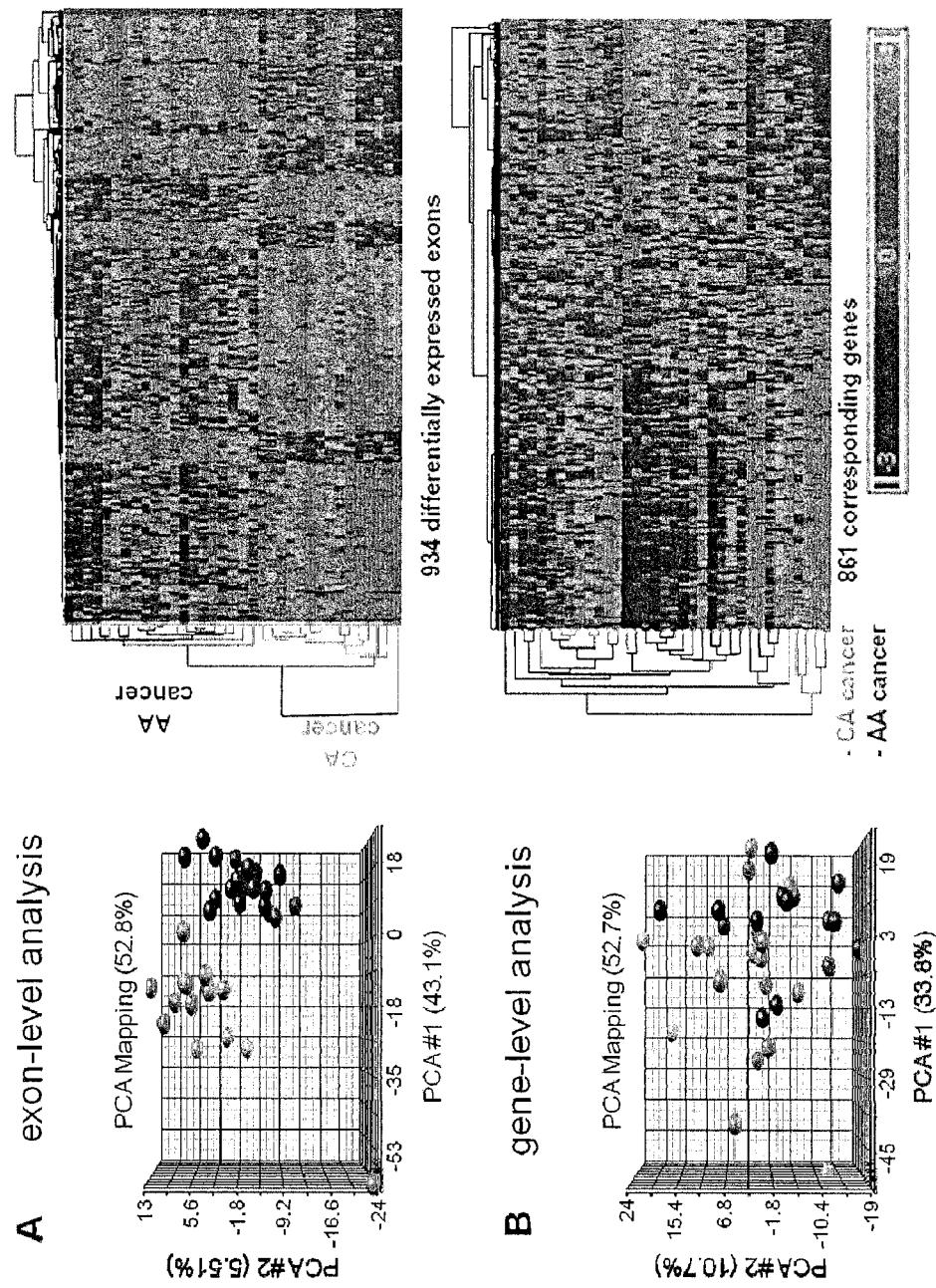


FIGURE 1

**FIGURE 2**

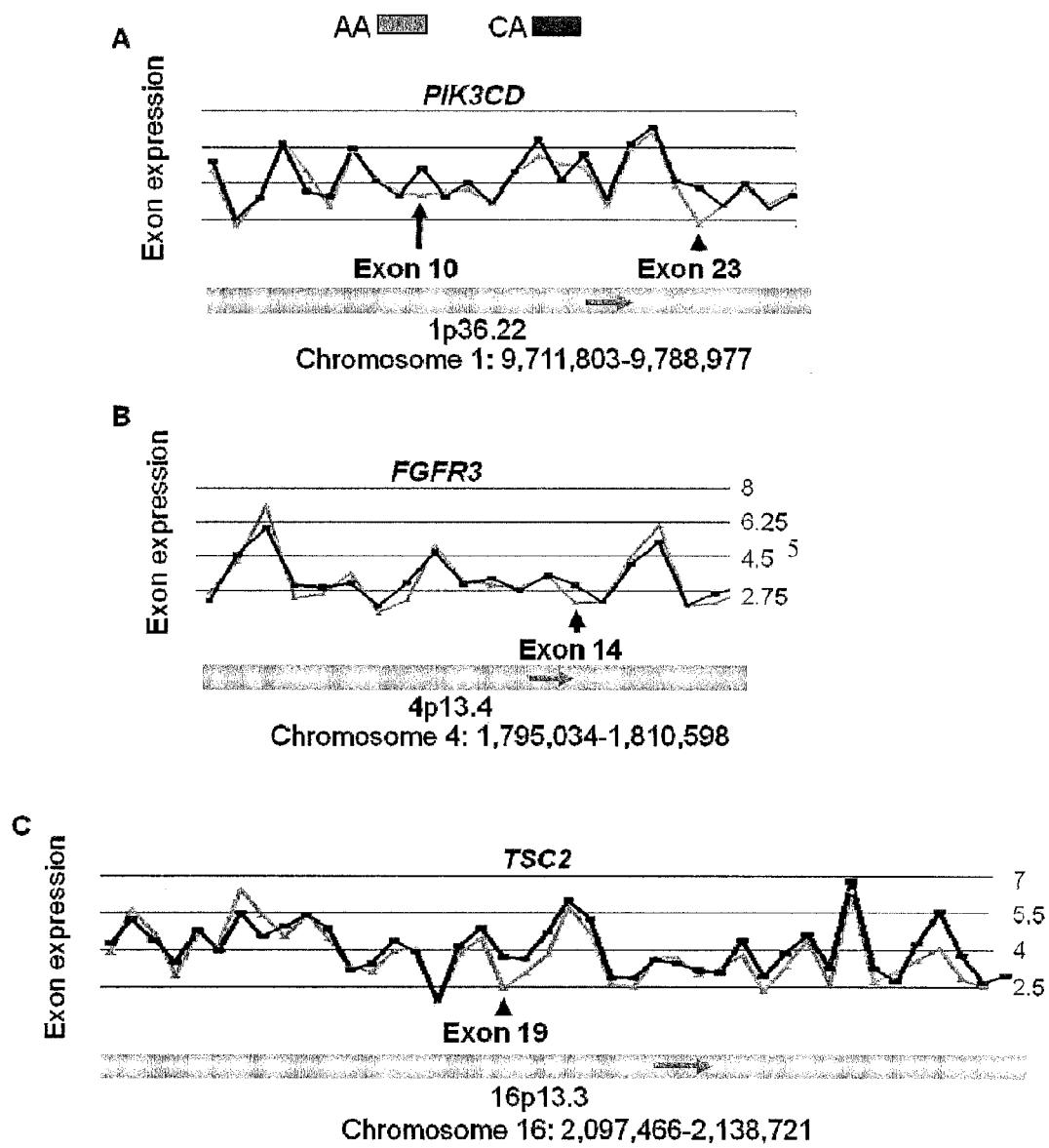


FIGURE 3

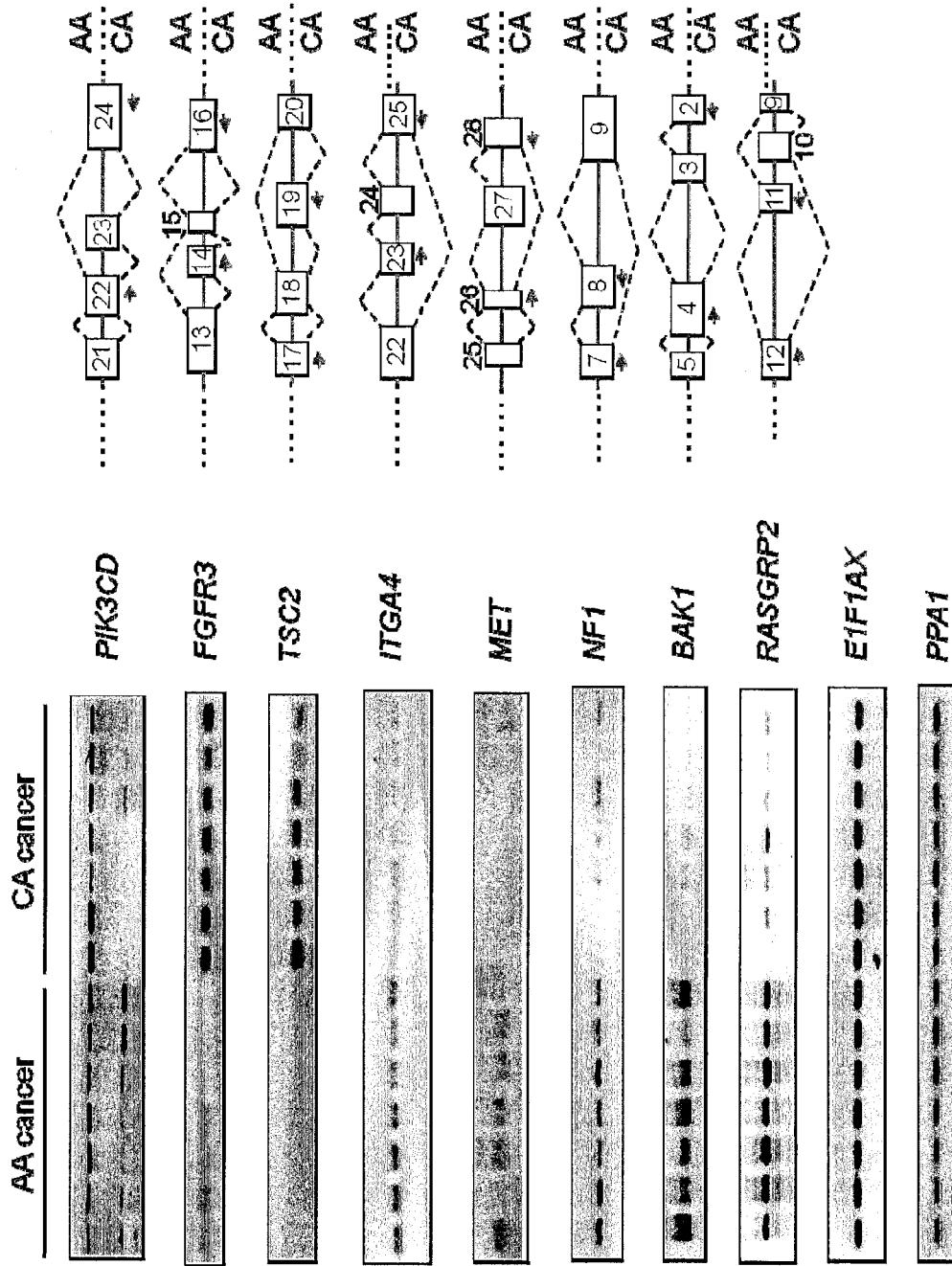


Fig. 4

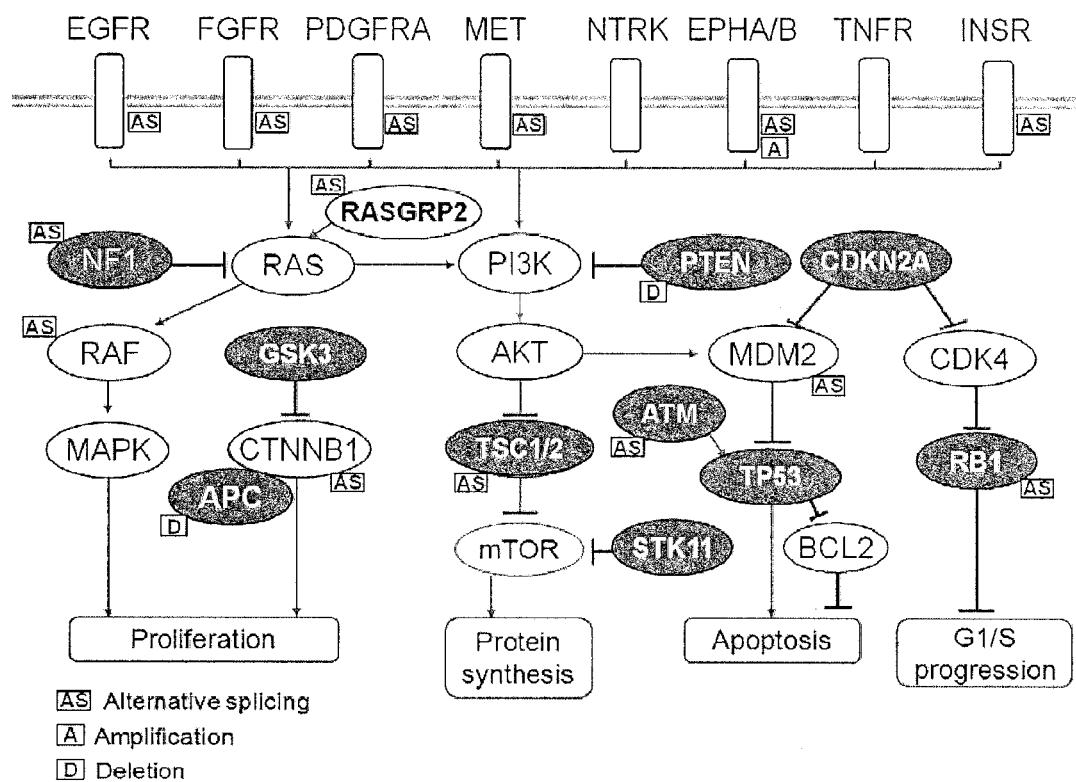


FIGURE 5

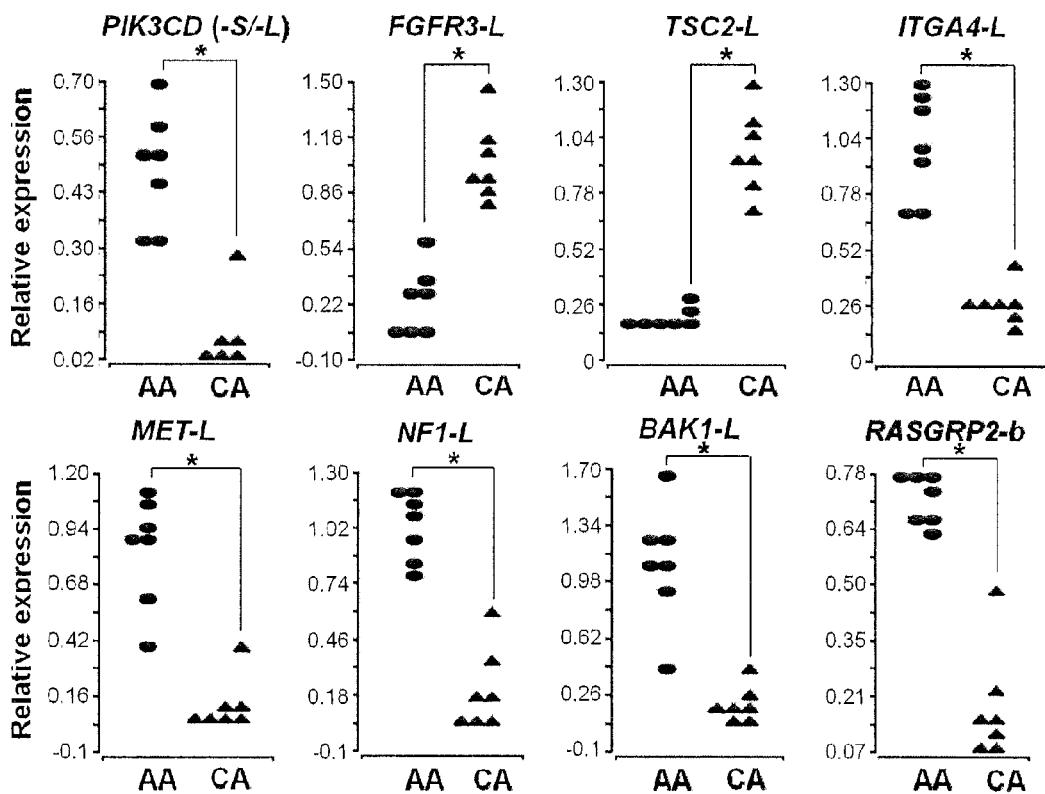
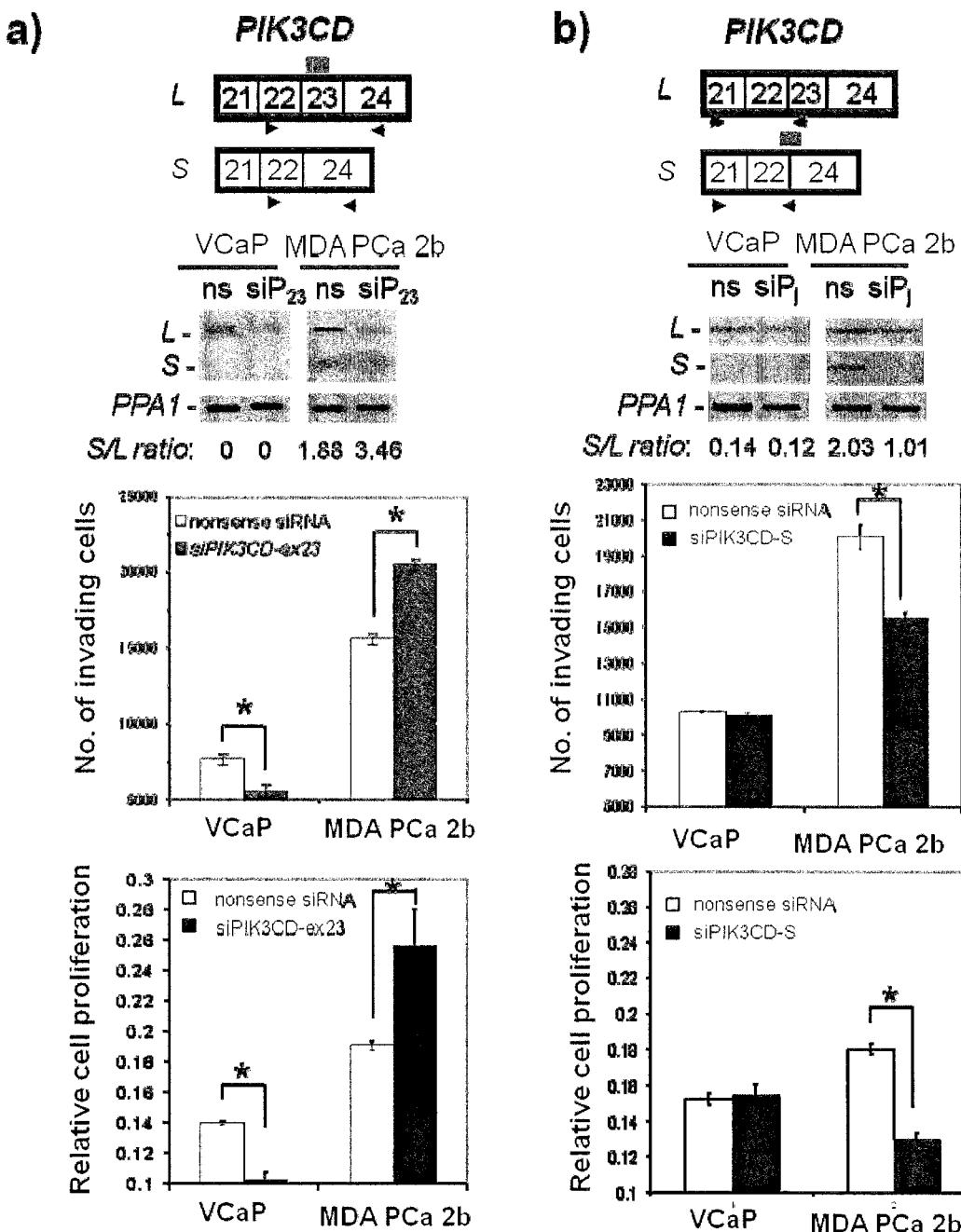
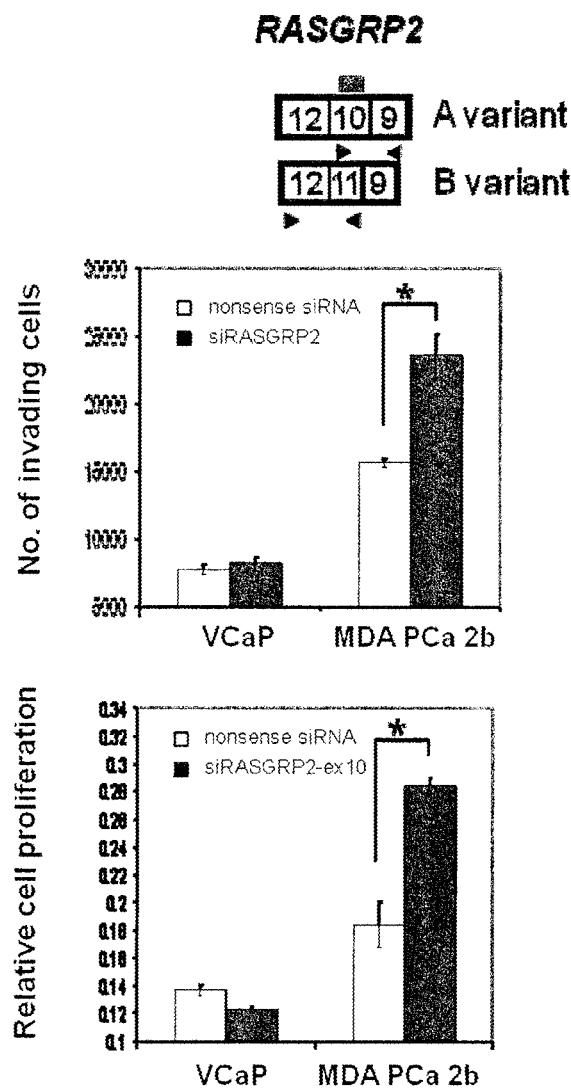
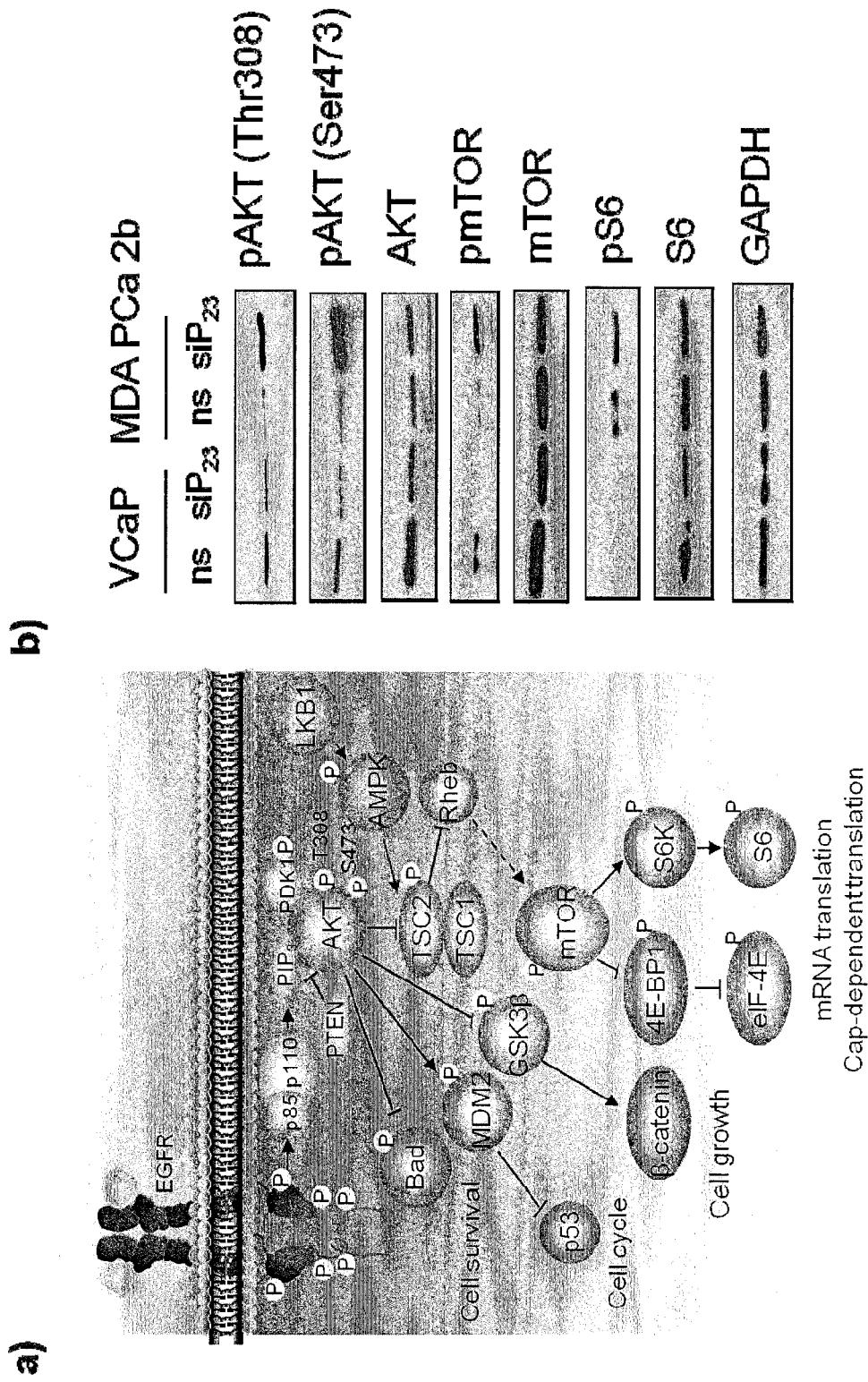


FIGURE 6

**FIGURE 7**

**FIGURE 8**

**Fig. 9**

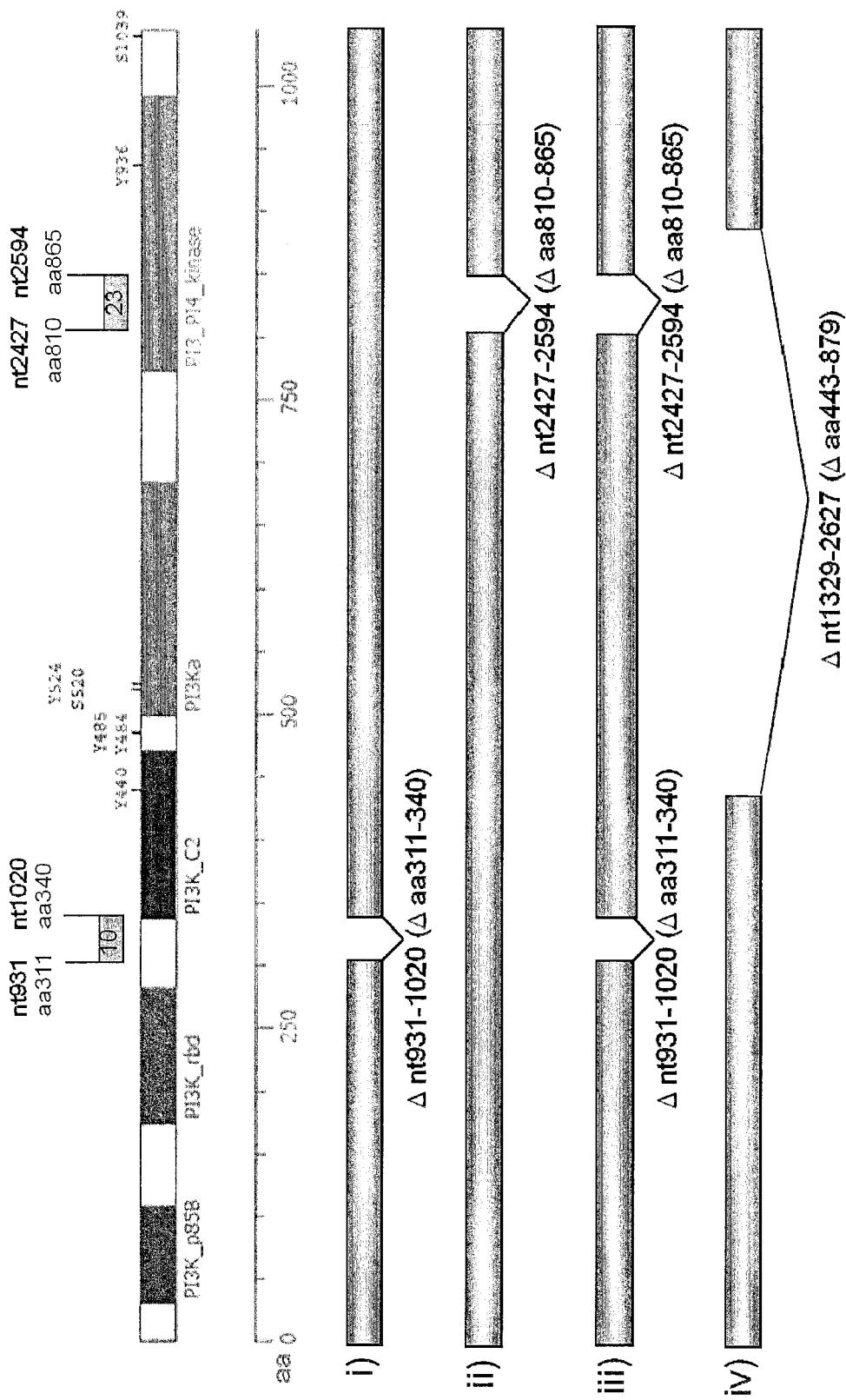


FIGURE 10

1

ALTERNATIVE SPLICING VARIANTS OF GENES ASSOCIATED WITH PROSTATE CANCER RISK AND SURVIVAL

REFERENCE TO RELATED APPLICATION

This application is a National Phase of International Application No. PCT/US2012/056346, filed Sep. 20, 2012, which claims priority to U.S. Provisional Patent Application No. 61/536,957, filed Sep. 20, 2011, which is incorporated herein by reference.

GOVERNMENT RIGHTS

This invention was made with government support under R01-CA120316, R01-DK056108, and 5U01-CA-116937 awarded by the NIH. The U.S. Government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention relates to novel splicing variants of a number of genes associated with prostate cancer risk and survival, and also the risk assessment, detection, diagnosis, or prognosis of prostate cancer (CaP). More specifically, this invention relates to the detection of certain splicing variants in genes PIK3CD, FGFR3, TSC2, ITGA4, MET, NF1, BAK1, and RASGRP2 to determine the risk, detect, diagnose, or prognosticate prostate cancer, particularly in the African American population. Research for the present invention was supported in part by American Cancer Society grant ACS-IRG-08-091-01.

BACKGROUND OF THE INVENTION

Prostate cancer (PCa) is the most common form of cancer among males. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

There are striking population (race) disparities in prostate cancer risk and survival outcome borne out of current health statistics data. This is particularly evident between African Americans (AA) and their Caucasian American (CA) counterparts. Epidemiologic studies have shown that higher mortality and recurrence rates of prostate cancer are still seen in AA men even after adjustment for socioeconomic status, environmental factors and health care access. Thus, it is likely that intrinsic biological differences account for some of the cancer disparities. Identifying these differences has been identified as a high-priority research area by the NIH, NCI and the Center to Reduce Cancer Health Disparities (CRCHD).

There are currently very few diagnostics methods available for the diagnosis and prevention of prostate cancer, particularly which can be used as predictor of risk and survival in African American population. Thus, the identification of genetic differences between AA and their CA counterparts, that are responsible for predisposition of prostate cancer would provide for a better understanding of the mechanisms of cancer causation (including ethnic and individual susceptibility), and ultimately lead to ways of prostate cancer prevention.

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SUMMARY OF THE INVENTION

Prostate cancer (PCa) is a disease conferred by multiple gene mutations, numerous alternations in gene expression and aberrant changes in genome composition/architecture. The African American (AA) population exhibits higher incidence and mortality rates compared to Caucasian Americans (CA). The present invention, through systematic mRNA expression profiling, characterizes the global mRNA expression profiles in AA and CA prostate tissue samples. A large number of genes are shown to have differential expression between AA and CA patients. Notably, several genes residing within the 5 oncogenic signaling pathways have been identified as exhibiting differential splicing, which includes but not limited to PIK3CD, FGFR3, TSC2, FGFR2, PDGFRA, ITGA4, MET, EPHA3, NF1, RASGRP2, CTNNB1, TSC2, ATM, CDK4, and RB 1 between AA and CA PCa specimens. Quantitative analysis of the expression profiles of PIK3CD, FGFR3, TSC2, RASGRP2, ITGA4, MET, NF1 and BAK1 in prostate samples confirm differential splicing between the AA and CA patients. With certain splicing variants predominantly exist in AA patients. As a non-limiting example, PIK3CD is expressed predominantly as a long variant in CA patients, whereas the AA patient would have higher portion of a short variant. The alternatively spliced short variant of PIK3CD is found to be a more aggressive form. Increasing the short to long variants ratio in a PCa cell line (MDA PCa 2b) that is representative to the AA PCa PIK3CD expression profile, by knocking down PIK3CD long variant expression increases cell proliferation and cell migration. Selectively knocking down the expression of PIK3CD short variant in the same cell line, decreases the short to long variants ratio, and results in marked decrease of cell proliferation and cell migration. Similarly AA predominant variants of FGFR3, TSC2 and RASGRP2 are also shown to be the more aggressive variant.

It is thus discovered by the inventors that alternative splicing variants for genes in the oncogenic signaling pathways, such as PIK3CD, FGFR3, TSC2, FGFR2, PDGFRA, ITGA4, MET, EPHA3, NF1, RASGRP2, CTNNB1, TSC2, ATM, CDK4, and RB1 are strong predictors of prostate cancer risk and survival, particularly in the AA patient population. It is thus an aim of the present invention to predict the risk and survival of a patient, by detecting the presence or absence of AA predominant variants of the genes in the oncogenic signaling pathways, particularly for PIK3CD, FGFR3, TSC2, FGFR2, PDGFRA, ITGA4, MET, EPHA3, NF1, RASGRP2, CTNNB1, TSC2, ATM, CDK4, and RB1, and more particularly for PIK3CD, FGFR3, TSC2, RASGRP2, ITGA4, MET, NF1 and BAK1. It is also an aspect of the present invention to utilize relative proportions of splicing variants of a certain gene as a predictor for PCa risk and survival in a patient.

Another aspect of the present invention is directed to isolated polynucleotide sequences of novel splicing variants of PIK3CD, FGFR3, TSC2, RASGRP2, ITGA4, MET, NF1 and BAK1. These novel splicing variants are particularly useful for the detection of the presence or absence of splicing variants in these genes that are in oncogenic signaling pathways. Detection of the presence or absence of splicing variants may be by polymerase chain reaction, by oligonucleotide probes hybridization, particularly high throughput DNA micro array analysis, or high throughput DNA sequencing, or any other means known to one skilled in the art. The isolated novel splicing variants sequences are also useful for targeted silencing of certain splicing variants

of these genes. Targeted gene silencing may be by siRNA, miRNA, or other complementary RNA constructs.

Additionally, polypeptide products of the novel splicing variants of the present invention may be analyzed for determining the presence or absence of certain splicing variants. Mass spectrometry may be used to identify peptide fragments specific to certain splicing variants. Antibodies specifically recognize specific amino acid sequences of the novel splicing variants may be developed for the detection of the protein products of these splicing variants. The antibodies may be monoclonal antibodies, polyclonal antibodies, Fab, single chain antibody, or other engineered antibody constructs known to one skilled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic drawing for prostate biopsy core sampling;

FIG. 2 shows differentially expressed exons between AA and CA populations;

FIG. 3 shows differential splicing events in AA and CA PCa specimens;

FIG. 4 shows quantitative RT-PCR validation of differentially expressed exons in AA and CA specimens;

FIG. 5 illustrates alternative splicing events were found in various signaling molecules in the cell survival and proliferation pathways;

FIG. 6 shows relative expression levels of PIK3CD, FGFR3, TSC2, ITGA4, MET, NF1, BAK1, and RASGRP2 splicing variants;

FIG. 7 shows the effect of PIK3CD splicing variants on cell proliferation and invasion;

FIG. 8 shows effect of knockdown RASGRP2 splicing variants on cell proliferation and invasion;

FIG. 9 shows effect of knockdown PIK3CD “long” variant on the AKT pathway; and

FIG. 10 shows 4 novel PIK3CD variants.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Alternative splicing dramatically expands the protein coding repertoire of higher eukaryotes. Current estimates suggest that greater than 60% of all human genes have more than one isoform/splice variant. The expression of specific splice variants is regulated in a developmentally and tissue-specific manner (Black DL: Mechanisms of alternative pre-messenger RNA splicing. Annu Rev Biochem 2003, 72:291-336). Alternatively spliced isoforms from the same gene can produce proteins with drastically different properties. For example, the bcl-x gene utilizes different 5' splice sites, resulting in proteins that have antagonistic functions. The short form of bcl-x promotes apoptosis, while the long form inhibits cell death (Boise L H, Gonzalez-Garcia M, Postema C E, Ding L, Lindsten T, Turka L A, Mao X, Nunez G, Thompson CB: bcl-x, a bcl-2-related gene that functions as a dominant regulator of apoptotic cell death. Cell 1993, 74:597-608).

Characterization of Clinical Specimens

Needle biopsy cores were collected by GWU Medical Faculty Associates urologists from right-base, left-base, right-mid, left-mid, right-apex, left-apex, right-transition, and left-transition zones of the prostate gland of individual patients presenting with high serum levels (>7 ng/ml) of prostate specific antigen (PSA). A schematic for 18 core biopsy is shown in FIG. 1. Collected cores were immediately examined by a board certified PCa pathologist. PCa

cores were determined to have a pathologic tumor stage of 2, and Gleason scores ranging from 6-9. There was no significant difference between the two racial groups (AA versus CA) with respect to age and tumor grade. Paired normal biopsy cores were also available from the same patients for genomic analysis (normal cores typically 1-2 cm away from cancer cores and deemed cancer free by pathologists). Each core contains sufficient RNA material for Affymetrix Human Exon 1.0 ST GeneChip profiling (i.e. 1 µg total RNA).

Exon Expression Profiling of AA and CA PCa and Normal Specimens

Total RNA was isolated from PCa and paired normal prostate cores. Exon profiling was performed on the Affymetrix Human Exon 1.0 ST GeneChip. The GeneChip represents an optimal platform for both expression profiling and splice variant detection (Kwan T, Benovoy D, Dias C, Gurd S, Provencher C, Beaulieu P, Hudson T J, Sladek R, Majewski J: Genome-wide analysis of transcript isoform variation in humans. Nat Genet 2008, 40:225-231; Network TCGAR: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 2008, 455: 1061-1068), as exon level annotations are derived from empirically determined, highly curated mRNA sequences and ab-initio computational predictions (see www.affymetrix.com/support/technical/whitepapers.affx). The GeneChip contains approximately 5.4 million 5-1 µm features (probes) grouped into 1.4 million probe sets interrogating over one million exon clusters. A 4-way statistical design (t-test with 10% false discovery rate (FDR) for multiple test correction) was employed to identify differentially expressed exons (corresponding to differentially expressed splice variants) in the following comparisons: AA normal vs. CA normal, AA cancer vs. CA cancer, AA cancer vs. AA normal, and CA cancer vs. CA normal. See FIG. 1A for comparison of AA cancer vs. CA cancer at the exon level.

The inventor through exon level analysis has identified 861 genes (e.g. PIK3CD, FGFR3, TSC2, RASGRP2, ITGA4, MET, NF1 and BAK1) exhibiting differential splicing patterns between the AA and CA populations. Differentially expressed exons between AA and CA populations are shown in FIG. 2. FIG. 2(A) shows Principle Components Analysis (PCA) plots and clustering analysis of differentially expressed exons between AA and CA PCa specimens. 20 AA and 15 CA PCa specimens were analyzed for global alternative splicing patterns (i.e. differentially expressed exons) using the Affymetrix human Exon 1.0 ST arrays. These splice variants represent candidate markers mediating PCa disparities. An example of a gene exhibiting population-specific splicing is integrin α4 (ITGA4) which has been postulated to be a metastasis suppressor, since blocking its activity with antisense RNA enhances oral squamous carcinoma cell motility (Zhang Y, Lu H, Dazin P, Kapila Y: Functional differences between integrin alpha4 and integrins alpha5/alphaV in modulating the motility of human oral squamous carcinoma cells in response to the V region and heparin-binding domain of fibronectin. Exp Cell Res 2004, 295:48-58.).

FIG. 3 shows relative expression of individual exons of PIK3CD, FGFR3, and TSC2 in AA and CA prostate cancers. FIG. 3(a) shows PIK3CD (phosphoinositide-3-kinase, catalytic, delta polypeptide) variants expression, FIG. 3(b) shows FGFR3 (fibroblast growth factor receptor 3) variants expression, and FIG. 3(c) shows TSC2 (tuberous sclerosis 2). Arrows indicate exons that are missing in the AA variant but present in the CA variant for each gene. Specifically, PIK3CD variants that lack exons 10 and 23, FGFR3 variant

lack exon 14, and TSC2 variant lacks exon 19 are more prevalent in AA PCa patients.

FIG. 4 shows quantitative RT-PCR validation of differentially expressed exons in AA and CA specimens. AA and CA patient samples are analyzed using quantitative RT-PCR, using primers listed in Table 1. Preferential expression of a particular exon in either AA or CA PCa specimens for the PIK3CD, FGFR3, TSC2, ITGA4, MET, NF1, BAK1, and RASGRP2 genes is seen. E1F1AX and PPA1 served as internal RT-PCR control genes, which are expressed equally in AA and CA PCa specimens.

TABLE 1

Primers for qRT-PCR validations of splice variants (-L and -S forms)	
PIK3CD	Primer-f (SEQ ID No. 2) : CAAACTGAAGGCCCTGAATGA Primer-r (SEQ ID No. 3) : TCTCGGATCATGATGTTGTGCG
FGFR3	Primer-f (SEQ ID No. 20) : ACAAACGTGATGAAAGATCGCA Primer-r (SEQ ID No. 21) : AGGTCGTGTTGCAGTTGG
TSC2	Primer-f (SEQ ID No. 29) : TTTGACTTCTGTTGCTGCT Primer-r (SEQ ID No. 30) : TGAGCACTTATAGCGCAG
RASGRP2	Primer-f (SEQ ID No. 38) : TCACCGGTGTCCTGGATCAGT Primer-r (SEQ ID No. 39) : CCACCATCTCTCGATGTGCT
ITGA4	Primer-f (SEQ ID No. 53) : TCTTGCTGTTGGGAGTATGAA Primer-r (SEQ ID No. 54) : TGATACTGAGGTCTCTTCCG
MET	Primer-f (SEQ ID No. 66) : TGGTGAAAAGAACCTCTCAA Primer-r (SEQ ID No. 67) : ATCTTGGCTCACTGCAACCT
NF1	Primer-f (SEQ ID No. 71) : GCATTTGGAACCTGGGTAGAA Primer-r (SEQ ID No. 72) : AACACCATGGACTGAACAA
BAK1	Primer-f (SEQ ID No. 80) : CCTGTTGAGAGTGGCATCAA Primer-r (SEQ ID No. 81) : TTGATGCCACTCTAAACAGG

Recently, genome sequencing efforts as part of the Cancer Genome Atlas Project has demonstrated that a number of genes (e.g. RAS, PTEN, p53, PI3K, APC, etc.) exhibiting frequent mutational hits in cancers can be found primarily residing in 3-5 major signaling pathways (Network TCGAR: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 2008, 455: 1061-1068; Parsons D W, Jones S, Zhang X, Lin J C, Leary R J, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia G L, et al: An integrated genomic analysis of human glioblastoma multiforme. *Science* 2008, 321:1807-1812; Ding L, Getz G, Wheeler D A, Mardis E R, McLellan M D, Cibulskis K, Sougnez C, Greulich H, Muzny D M, Morgan M B, et al: Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* 2008, 455:1069-1075). Of interest from a cancer disparities perspective is our observation that many of these same genes are prone to population-specific splicing patterns. FIG. 5 indicates genes marked with (AS) define

differential alternative splicing events occurring in AA versus CA PCa. (Copy number amplifications (A) and deletions (D) are also indicated). At least 11 out of 26 genes residing in the 5 oncogenic signaling pathways have been identified by the inventors as exhibiting differential splicing between AA and CA PCa specimens. These genes include FGFR2, PDGFRA, MET, EPHA3, NF1, RASGRP2, CTNNB1, TSC2, ATM, CDK4, and RB1. The inventors further show that differential mRNA splicing in racial populations plays an important role in cancer health disparities.

FIG. 6 shows quantification of differential splicing in PIK3CD, FGFR3, TSC2, ITGA4, MET, NF1, BAK1, and RASGRP2 in AA and CA PCa patients. For each of these genes, one variant is predominant in AA patients. Also, proportions of variants, such as short and long form of PIK3CD are markedly different between AA and CA patients. AA patients have a higher S/L ratio than CA patients.

20 Functional Consequences of Splice Variants in PCa Cell Lines Derived from AA and CA Patients

Inventors demonstrate that the splice variant (short form or S variant) for phosphoinositide-3 kinase delta (PIK3CD) found in AA PCa specimens encodes a more aggressive version of the gene (i.e. leading to greater proliferation and invasion of cancer cells) compared to the variant counterpart (long form or L variant) found in CA PCa specimens (FIG. 7). In the CA PCa cell line VCaP, the L form is the only variant found, while very little to no expression of the S variant is seen (and hence the reason we refer to the L variant as the 'CA isoform') (FIG. 7A). The predominant expression of the L variant and very little to no expression of the S variant in the CA PCa cell line is consistent with the CA patient samples (see PIK3CD in FIG. 4). SiRNA-mediated knockdown of the L variant in VCaP cells leads to a decrease in Matrigel invasion and a decrease in proliferation (FIG. 7A). By comparison, the AA PCa cell line MDA PCa 2b expresses both an L and S variant, and knockdown of the L variant leads to an increase in Matrigel invasion and an increase in proliferation (FIG. 7A). Since VCaP cells express very little to no S variant, targeted siRNA-mediated knockdown of this variant leads to no change in Matrigel invasion and proliferation (FIG. 7B). In contrast, targeted knockdown of the S variant in MDA PCa 2b cells leads to decreased Matrigel invasion and decreased proliferation (since the S variant is found almost exclusively in AA patient samples, it is referred to as the 'AA variant') (FIG. 7B). These data indicate that the balance of S to L isoforms in MDA PCa 2b cells dictates the oncogenic profile of the AA PCa cell line. Namely, knocking down the L variant in MDA PCa 2b cells increases the S/L ratio, leading to a higher proportion of the aggressive S variant and consequently increased invasiveness and proliferation of the cell line. In contrast, knocking down the S variant in MDA PCa 2b cells decreases the S/L ratio, leading to a higher proportion of the less aggressive L variant and consequently decreased invasiveness and proliferation of the cell line. Analogous findings were obtained in MDA PCa 2b cells when the ratio of the 'AA variant' (S or isoform) was increased over the 'CA variant' (L or an isoform) for the FGFR3, TSC2.

For RASGRP2, the long variant (with exon 10) is common to both AA and CA patients, whereas the short variant (without exon 10) is unique to AA. Targeted knockdown of the long splicing variant in VCaP cells reduced Matrigel invasion and an increase in proliferation (FIG. 8). In contrast, target knockdown of the RASGRP2 long variant in MDA PCa 2b Cells has the opposite effect.

Activation of AKT is known to promote cell growth and mRNA translation (FIG. 9a). When the expression of PIK3CD “long” variant is knocked down by siRNA targeting of Exon 23 in the VCaP cell line, which only expresses the long variant, there is a decrease of phosphorylation of AKT, compared to nonsense siRNA control, and also decrease of phosphorylation of downstream signaling proteins mTOR and S6 (FIG. 9b). However, in MDA PCa 2b cells, which express the short variant of PIK3CD, knocking down the long variant of PIK3CD markedly increases AKT phosphorylation, both on Thr308 and Ser473, and increases phosphorylation of mTOR and S6 (FIG. 9b). In other words, increasing S/L variants proportion in MDA PCa 2b cells activates the AKT pathways.

The inventor discovered four novel PIK3CD variants (FIG. 10), where variant 1 lacks exon 10 (SEQ ID No. 7), which can be shown as the deletion of nt2430-2592 compared to full length PIK3CD cDNA sequence (SEQ ID No. 1), variant 2 lacks exon 23 (SEQ ID No. 11, deletion of nt931-1020), variant 3 lacks both exon 10 and 23 (SEQ ID No. 14, deletion of nt931-1020 and nt2430-2592), and variant 4 contains a deletion from nt1329-2627 (SEQ ID No. 16). The nucleotide sequence of PIK3CD full length cDNA sequence is shown in Table 2. Exon 10 and exon 23 are marked with double underline and wave underline, respectively. cDNA sequence of variants 1-4 (SEQ ID Nos. 7, 11, 14, and 16) are shown in Tables 3-6. Exemplary primers across the junctions of the splicing variants (SEQ ID Nos. 6, 10, and 15) that are useful for detecting the presence of these variants are shown in Table 7. Exemplary siRNAs for selective knockdown of PIK3CD full length (targeting exon 23, SEQ ID Nos. 4 and 5)) and variants (targeting exon junctions (SEQ ID Nos. 8, 9, 12, and 13) and deletion junction (SEQ ID Nos. 17 and 18)) are listed in Table 8.

The inventor also discovered a novel splicing variant of FGFR3 (fibroblast growth factor receptor 3), which lacks exon 14 (SEQ ID No. 19, Table 10). The nucleotide sequence of FGFR3 full length cDNA sequence (SEQ ID No. 19) is shown in Table 9. Exon 14 is marked with double underline. Exemplary primer across the junction of splicing variant (SEQ ID No. 26) that is useful for detecting the presence of this variant is shown in Table 11. Exemplary siRNAs for selective knockdown of FGFR3 full length (targeting exon 14, SEQ ID NOS. 22 and 23)) and variant (targeting exon junction (SEQ ID Nos. 26 and 27) are listed in Table 12.

The inventor also discovered a novel splicing variant of TSC2 (tuberous sclerosis 2), which lacks exon 19 (SEQ ID No. 34, Table 14). The nucleotide sequence of TSC2 full length cDNA sequence (SEQ ID No. 28) is shown in Table 12. Exon 19 is marked with double underline. Exemplary primer across the junction of splicing variant (SEQ ID No. 33) that is useful for detecting the presence of this variant is shown in Table 15. Exemplary siRNAs for selective knockdown of TSC2 full length (targeting exon 19, SEQ ID NOS. 31 and 32)) and variant (targeting exon junction (SEQ ID Nos. 35 and 36) are listed in Table 16.

The inventor also discovered two novel splicing variants of RASGRP2 (RAS guanyl-releasing protein 2), which lacks exon 10 (SEQ ID No. 45, Table 18) or exon 11 (SEQ ID No. 49, Table 19). The nucleotide sequence of RASGRP2 full length cDNA sequence (SEQ ID No. 37) is shown in Table 17. Exon 10 is marked with double underline, and exon 11 is marked with wave underline. Exemplary primers across the junctions of the splicing variants (SEQ ID Nos. 44 and 48) that are useful for detecting the presence of these variants are shown in Table 20. Exemplary siRNAs for selective knockdown RASGRP2 full length (targeting exon 10, SEQ ID NOS. 40 and 41, targeting exon 11, SEQ ID NOS. 42 and 43)) and variants (targeting exon junctions (SEQ ID Nos. 46, 47, 50, and 51)) are listed in Table 21.

The inventor also discovered a novel splicing variant of ITGA4 (integrin α4), which lacks exon 23 (SEQ ID No. 58, Table 23). The nucleotide sequence of ITGA4 full length cDNA sequence (SEQ ID No. 52) is shown in Table 22. Exon 23 is marked with double underline. Exemplary primer across the junction of splicing variant (SEQ ID No. 57) that is useful for detecting the presence of this variant is shown in Table 24. Exemplary siRNAs for selective knockdown of ITGA4 full length (targeting exon 23, SEQ ID NOS. 55 and 56)) and variant (targeting exon junction (SEQ ID Nos. 59 and 60)) are listed in Table 25.

The inventor also discovered a novel splicing variant of MET (MNNG HOS Transforming gene), which include the insertion of non-coding exon 27 (SEQ ID No. 65, Table 27). The nucleotide sequence of MET full length cDNA sequence (SEQ ID No. 62) is shown in Table 26. Exon 27 is marked with double underline. Exemplary primer across junctions of full length variant (SEQ ID No. 61) is shown in Table 28. Exemplary siRNAs for selective knockdown of MET full length (targeting exon junction 26 and 28 (SEQ ID Nos. 63 and 64) and variant (targeting exon 27 (SEQ ID Nos. 68 and 69)) are listed in Table 29.

The inventor also discovered a novel splicing variant of NF1 (Neurofibromin 1), which lacks exon 8 (SEQ ID No. 76, Table 31). The nucleotide sequence of NF1 full length cDNA sequence (SEQ ID No. 70) is shown in Table 30. Exon 8 is marked with double underline. Exemplary primer across the junction of splicing variant (SEQ ID No. 75) that is useful for detecting the presence of this variant is shown in Table 32. Exemplary siRNAs for selective knockdown of NF1 full length (targeting exon 8, SEQ ID NOS. 73 and 74) and variant (targeting exon junction (SEQ ID Nos. 77 and 78)) are listed in Table 33.

The inventor also discovered a novel splicing variant of BAK1 (Bcl-2 homologous antagonist/killer), which lacks exon 2 (SEQ ID No. 85, Table 35). The nucleotide sequence of BAK1 full length cDNA sequence (SEQ ID No. 79) is shown in Table 34. Exon 2 is marked with double underline. Exemplary primer across the junction of splicing variant (SEQ ID No. 84) that is useful for detecting the presence of this variant is shown in Table 36. Exemplary siRNAs for selective knockdown of BAK1 full length (targeting exon 2, SEQ ID NOS. 82 and 83) and variant (targeting exon junction (SEQ ID Nos. 86 and 87) are listed in Table 37.

TABLE 2

PIK3CD (Full length) Nucleotide Sequence (3135 nt, SEQ ID No. 1)
ATGCCCTGGGTGGACTGCCCATGGAATTCTGGACCAAGGAGGAGAATCAGAGCGTTGTGGTTGACT
TCCTGCTGCCACAGGGTCTACCTGAACCTCCCTGTGTCCCACATGCCAACCTCAGCACCATCAAGCA

TABLE 2 -continued

PIK3CD (Full length) Nucleotide Sequence (3135 nt, SEQ ID No. 1)

GTGCTGTGGACCGCGCCAGTATGAGGCCCTCTTCCACATGCTCAGTGCCCCGAGGCTATGTGTTCACTGCATCAACAGACAGCGGAGCAGCAAGAGCTGGAGGACGAGCAACGGCTGTGACGTGCAGCCTTCCTGCCCCGCTGGCTGGAGGCTGGCTGGCTGAAGAAGCTCATCAACTCACAGATCAGCCTCCTCATCGGAAAGGCCCTCACGAGTTGACTCCTTGTGCGACCCAGAAGTGAACGACTTCGCGCCAAGATGTGCAATTCTGCGAGGGAGGCGCCGCCGGCAGCAGCTGGCTGGAGGCTGGCTGCAGTACAGTTCCCCTGCGCTCAAACCTGGGGCTGGTACCCCTGCGGCTCCGAAAGGGCCCTCTGGTCAACGTTAACGTTGAGGGCAGCGAGGAGAGCTTCACCTTCAGGTGTCACCAAGGACGTGCTCCGGCAGCCGCTGGTGGACAGCCGGAAGACTACACGCTGCAGGTGAACGGCAGGCATGAGTACCTGTATGGCAGCTACCGCTCTGCCAGTTCAGTACATCTGCGAGTGCCTGCACAGTGGTTGACCCCTCACCTGACCATGGTCCATTCCCTCTCCATCTCGCCATGCGGATGAGCAGAGCAACCTGCCCTCAGGTCCAGAAACCGCGTGCCTAAACCCACCTCCCTGCGAAGAAGCCTCTGTGTCCTGGTCCGGAGCAGCCGTTCCGATCGAGCTCATCCAGGGCAGCAAAGTGAACGCCAGCGGGATGAAGCTGGTGGTGCAGGCCGGCTTTCCACGGCAACGAGATGCTGTCAGACGGTCCAGCTGGAGGCTGCTGAGCAGCAGCAGCTGGAGTTGACATCACACATCTGCGACCTGCCCTGCGATGGCCCTCTGCTTGGCCTGTACGCCGTGATCGAGAAAGCCAAGAAGGCTCGCTCCACCAAGAAGAAGTCCAAGAAGGCCAGTGCCTCCAGCCATTGCCCTGGCCAACCTCATGCTGTTGACTACAAGGACCAAGCTTAAGACGGGGAAACGCTGCCTCTACATGTGGCCCTCCGCTCCAGATGAGAAGGGCGAGCTGCTGAACCCACGGGACTGTGCGCAGTAACCCAAACACGGATAGCGCGCTGCCCTGCTCATCTGCGCTGCCGAGGGTGGCCCGCACCCCGTGTACTACCCGCCCTGGAGAAGATCTGGAGCTGGGGGACACAGCAGTGTGCACTGACCGAGGAGGAGCAGCTGCAGCTGCCGAAATCTGGAGCTGGGGGCTGGGGAGCTGTATGAGCACGAGAAGGACCTGGTGTGGAAGCTGCCGATGAAGTCCAGGAGCATTCCCGAGGCGCTAGCCCGCTGCTGCTGGTACCAAGTGGAAACAGCATGAGGATGTGGCCAGATGCTACCTGCTGTGCTCCCTGGCCGAGCTGGCCCTCTGAGCGCCCTGGAGGCTGCTAGACTTCAGCTCCCGATTGCCACGTAGGCTCCTTCGCCATCAAGTCGCTGCCGAAACTGACGGACGATGAGCTGTTCCAGTACCTGCTGCACTGGTCAGGGTGTCAAGTACGAGCTCCTACCTGGACTGCGAGCTGACCAAATTCCCTGCTGGACCGGGCCCTGGCCAACCGCAAGATCGGCCACTTCCTTCTGGCACCTCGCTCCAGATGACGCGTGGCGTGGCATCTTAAAGAACGGGGATGACCTCCGGCAGGACATGCTGACCCCTGAGATGATCCAGCTCATGGACGTCTGGTAAGCAGGGGAAGCACTGAGCAAACTGAAGGCCCTGAATGACTCGTCAAGCTGAGCTCTCAGAAGACCCCCAAGCCCCAGACCAAGGAGCTGATGCACTTGTGCACTGCCGAGGAGCCT

TABLE 2 -continued

PIK3CD (Full length) Nucleotide Sequence (3135 nt, SEQ ID No. 1)

TCAACCTACGACTTGTCCATGTGATTTCAGCGGGAAAGACTAATAATAGTTGAGAAATTGACCGTTCCG
 GGGCTACTGTGAAAGGGCCTACACCACCTGCAGCGCCACGGGCTCTCTCCACCTCTTGCCCTG
 ATGCAGGGCGGCAGGCTGCCTGAGCTCAGCTGCTCAAAGACATCCAGTATCTCAAGGACTCCCTGGCAC
 TGGGGAAAACAGAGGAGGAGGACTGAAGCACTCCGAGTGAAGTTAACGAAGCCCTCGTGAGAGCTG
 GAAAACCAAAGTGAACGGCTGGCCACAACGTGTCAGAACAGGCAGTAG

(Exon 10 is indicated by double underline, Exon 23 is indicated by wave underline. Primers for qRT-PCR validations of PIK3CD splice variants (-L and -S forms) are underlined)

TABLE 3

PIK3CD variant 1 (lacking exon 10) Nucleotide Sequence (3045 nt, SEQ ID No. 7)

ATGCCCTGGGTGGACTGCCCATGGAATTCTGGACCAAGGAGGAGAATCAGAGCGTTGGTTGACT
 CCTGCTGCCACAGGGTCTACCTGAACCTCCCTGTGTCCCACATGCCAACCTCAGCACCATCAAGCA
 GCTGCTGTCACCGCGCCAGTATGAGCCGCTCTCCACATGCTCAGTGGCCCCGAGGCCTATGTGTC
 ACCTGCATCAACAGACAGGGAGGAGCAAGAGCTGGAGGAGGAGCAACGGCTCTGTGACGTGCA
 CCTTCTGCCGCTCGCCTGGTGGCCGAGGGCGACCGCGTGAAGAACGCTCATCAACTCACAGAT
 CAGCCTCCTATCGCAAAGGCCACGAGTTGACTCCTGTGCGACCCAGAAGTGAACGACTTCGC
 GCCAAGATGTGCAATTCTGAGGGAGGCGCCGCCCCGGCAGCAGCTGGCTGGAGGCCCTGGCTGC
 AGTACAGTTCCCCCTGAGCTGGAGCCCTGGCTCAAACCTGGGGCTGGTACCTGCGGCTCCGAA
 CGGGCCCTTCTGGTCAACGTTAAGTTGAGGGCAGCGAGGAGGAGCTTACCTTCAGGTGTCACCAAG
 GACGTGCCGCTGGCCTGATGGCTGTGCCCTGCGGAAGAAGGCCACAGTGTCCGGCAGCCGCTGGTGG
 AGCAGCCGAAAGACTACACGCTGCAGGTGAACGGCAGGAGTACCTGTATGGCAGCTACCGCTCTG
 CCAGTTCCAGTACATCTGAGCTGCCCTGCACAGTGGTTGACCCCTCACCTGACCATGGTCAATTCTCC
 TCCATCTGCCATGCCGATGAGCAGAGCAACCCCTGCCCTCAGGTCCAGAACCGCGTGCACAAAC
 CTCCATTCCTGCGAAGAAGCTGGTGGTGCAGGCCGGCTTCCACGGCAACGAGATGCTGTGCAAGACGG
 TGTCAGCTGGAGGTGAGCGTGTGCTGGAGCCCGTGTGGAAGCAGCGGCTGGAGTTCGACATCAACATCT
 GCGACCTGCCCGCATGGCCGCTCTGCTTGCCTGTACGCCGTGATCGAGAAAGCCAAGAAGGCTCGCT
 CCACCAAGAAGAAGTCCAAGAAGGGCGACTGCCCTGCCTGGCCACCTCATGCTGTTGACTACAAGG
 ACCAGCTTAAGACCGGGAACGCTGCCCTACATGTGCCCTCCGAGATGAGAAGGGGAGCTGCTGA
 ACCCCACGGGACTGTGCGCAGTAACCCCAACACGGATAGCCGCTGCCCTGCTCATCTGCCCTGCCGAGG
 TGGCCCGCACCCGTGTAACCCCGCCCTGGAGAAGATCTGGAGCTGGGGGAGACAGCGAGTGTGTC
 ATGTCACCGAGGAGGAGCAGCTGCAGCTGCGGAAATCCTGGAGCGGGGGCTGGGGAGCTGTATGAGC
 ACGAGAAGGACCTGGTGTGGAAGCTGGCATGAAGTCCAGGAGCACTCCGGAGGCGTAGCCGGCTG
 TGCTGGTACCAAGTGGAACAGCATGAGGATGTGCCAGATGCTCACCTGCTGTGCTCTGCCGGAGC
 TGCCCGTCTGAGCGCCCTGGAGCTGCTAGACTTCAGCTTCCGATTGCCACGTAGGTGCTCCCTGCC
 AGTCGCTGCCGAAACTGACGGACGATGAGCTGGTCCAGTACCTGCTGAGCTGGTGCAGCTGGTGC
 AGTCCCTACCTGGACTGCGAGCTGACCAAATTCTGCTGGACCGGGCCCTGGCCAACCGCAAGATCG
 CCTTTCTGGCACCTCCGCTCGAGATGCACTGCGTGGCCCTGCGCTTGGCCTCATCTGGAGG
 CCTACTGCAGGGCAGCACCCACCATGAAGGTGCTGATGAAGCAGGGGAAGCAGTGAAGCAACTGA
 CCCTGAATGACTCGTCAAGCTGAGCTCTCAGAAGACCCCCAGACCAAGGAGCTGATGCACTTGT

TABLE 3 -continued

 PIK3CD variant 1 (lacking exon 10) Nucleotide Sequence
 (3045 nt, SEQ ID No. 7)

GCATGCGGCAGGAGGCCAACCTAGAGGCCCTCCCACCTGCAGTCCCCACTCGACCCCAGCACCCCTGCTGG
 CTGAAGTCGCTGGAGCAGTGCACCTTCATGGACTCCAAGATGAAGGCCCTGTGGATCATGTACAGCAACG
 AGGAGGCAGGCAGGGGGCAGCGTGGGCATCATCTTAAGAACGGGATGACCTCGGCAGGACATGCTGA
 CCTGCAGATGATCCAGCTATGGACGCTGTGGAAAGCAGGAGGGCTGGACCTGAGGATGACCCCTATG
 GCTGCCTCCCCACCGGGGACCGCACAGGCCTCATTGAGGTGGTACTCCGTTCAGACACCATGCCAACATCC
 AACTCAACAAGCAACATGGCAGCACAGGCCCTCAACAAGGATGCCCTGCTCAACTGGCTGAAGTCCA
 AGAACCCGGGGAGGCCCTGGATCGAGCATTGAGGAGTTCACCCCTCCTGTGCTGGCTATTGTGTGGCA
 CATATGTGCTGGCATTGGCATCGGCACAGCGACAACATCATGATCCGAGAGAGTGGGAGCTGTTCCACA
 TTGATTTGGCCTTTCTGGGAATTCAAGACCAAGTTGGAATCAACCGCGAGCGTGTCCCATTCA
 TCACCTACGACTTGTCCATGTGATTCAAGCAGGGAAAGACTAATAATAGTGAGAAATTGAAACGGTTCCGG
 GCTACTGTGAAAGGCCAACCCATCCTGCGCGCCACGGGCTTCCTCCTCCACCTCTTGCCCTGATGC
 GGGCGCAGGCCCTGCTGAGCTCAGCTGCTCAAAGACATCCAGTATCTCAAGGACTCCCTGGACTGGGA
 AACACAGGAGGAGGAGGACTGAAGCCTCCGAGTGAAGTTAACGAGGCCCTCGTGAGAGCTGGAAAACCA
 AAAGTGAACCTGGCTGGCCACACGTCTCAAAGACACAGGAGTAG

(Double underline indicates bases bordering the splice junction)

TABLE 4

 PIK3CD variant 2 (lacking exon 23) Nucleotide Sequence
 (2967 nt, SEQ ID No. 11)

ATGCCCTGGGTGGACTGCCCATGAAATTCTGGACCAAGGAGGAGAACAGAGCGTTGTGGTTGACT
 CCTCTGCTGCCAACAGGGTCTACCTGAACCTCCCTGTGTCGGCAATGCCAACCTCAGCACCATCAAGCA
 GCTGCTGTGGCACCGGCCAGTATGAGCCGCTCTTCCACATGCTCAGTGGCCCCAGGGCTATGTGTT
 ACCTGCATCAACAGACAGCGGAGCAGCAAGAGCTGGAGGAGGAGCAACGGCTGTGACGTGAGC
 CCTTCCCTGCCGCTCTGCGCTGGTGGCCGTGAGGGCGACCGCGTGAAGAACGCTCATCAACTCACAGAT
 CAGCCTCCTCATCGCAAGGCCCTCACGAGTTGACTCCTGTGCGACCCAGAAGTGAACGACTTCGC
 GCCAAGATGTGCAATTCTGCAGGAGGCGCCGCCGGCAGCAGCTGGCTGGAGGGCTGGCTGCC
 AGTACAGTTCCCCCTGAGCTGGAGGCCCTCGCTCAAACCTGGGGCTGGTACCCCTGCGGCTCCGAA
 CGGGCCCTCTGGTCAACGTTAAGTTGAGGGCAGCGAGGAGAGCTTACCTTCAGGTGTCCACCAAG
 GACGTGCGCGCTGGCCTGATGGCCTGTGCCCTGCGGAAGAAGGCCACAGTGTCCGGCAGCCGCTGGTGG
 AACAGCGGAAAGACTACACGCTGCAGGTGAACGGCAGGCATGAGTACCTGTATGGCAGCTACCGCTCTG
 CCAGTCCAGTACATCTGCAGCTGCCCTGCAACAGTGGTTGACCCCTCACCTGACCATGGTCCATTCTCC
 TCCATCCTGCCATGCCGATGAGCAGAGCAACCTGCCCGGAGTCCAGAAACCGCGTGCACAAACAC
 CTCCCATCCTGCCGAGAAGGCCCTCTGTGTCCTGTGGTCCCTGGAGCAGCCGTTCCGACATCGAGCT
 CATCCAGGGCAGCAAAGTGAACGCCAGCGGGATGAAGCTGGTGTGCGAGGCCGGCTTCCACGGC
 AACGAGATGCTGTGCAAGACGGTGTCCAGCTGGAGGTGAGCGTGTGCTGGAGCCGTTGGAAGCAGC
 GGCTGGAGTTGACATCAACATCTGCGACCTGCCCGCATGGCCGCTCTGCTTGCCTGTACGCC
 GATCGAGAAAGCCAAGAAGGCTGCTCCACCAAGAAGAAGTCCAAGAAGGCCAGTGCCTCTACATGTGCC
 GCCAACCTCATGCTGTTGACTACAAGGACCAAGCTTAAGACGGGGAAACGCTGCCCTACATGTGCC
 CGTCCCAGATGAGAAGGGCGAGCTGCTGAACCCACGGGACTGTGCGCAGTAACCCAAACACGGATAG

TABLE 4-continued

PIK3CD variant 2 (lacking exon 23) Nucleotide Sequence
(2967 nt, SEQ ID No. 11)

CGCCGCTGCCCTGCTCATCTGCCCTGCCGAGGTGGCCCCGCACCCCGTGTACTACCCGCCCTGGAGAAG
ATCTGGAGCTGGGGCAGACACAGCAGTGTGTCATGTCACCGAGGAGGAGCAGCTGCAGCTGCGGGAAA
TCCTGGAGCGGGGGGGTCTGGGGAGCTGTATGAGCACGAGAAGGACCTGGTGTGGAAGCTGCCGATGA
AGTCAGGAGGACTTCCGGAGGCCTAGCCGGCTGCTGGTGTACCAAGTGGAAACAGCATGAGGAT
GTGGCCAGATGCTCTACCTGCTGTGCTCTGGCGAGCTGCCGTCTGAGGCCCTGGAGCTGCTAG
ACTTCAGCTTCCCAGATTGCCACGTTAGGCTCTTCGCCATCAAGTCGCTGCCAGAACTGACGGACGATGA
GCTGTTCCAGTACCTGCTGCAGCTGGTGCTCAAGTACGAGTCTACCTGGACTGCGAGCTGACC
AAATTCTGCTGGACCGGGCCCTGGCCAACCGCAAGATGCCACTTCCTTCTGGCACCTCCGCTCG
AGATGCACGTGCCGTCGGTGGCCCTGCGCTTCGGCCTCATCTGGAGGCCTACTGCAGGGCAGCACCCA
CCACATGAAGGTGCTGATGAAGCAGGGGAAGCACTGAGCAAACGTGAAGGCCCTGAATGACTCGTCAAG
CTGAGCTCTCAGAAGACCCCCAAGCCCCAGACCAAGGAGCTGATGCACTTGTGCACTGCCAGGAGGCC
ACCTAGGGCCCTCTCCACCTGCACTCCCACTCGACCCAGCACCTGCTGGCTGAAGTCTGCTGGA
GCAGTGCACCTCATGGACTCCAAGATGAAGCCCCTGTGGATCATGTACAGCAACGAGGAGGCAGC
GGCGGAGCGTGGCATCATTTAAGAACGGGGATGACCTCCGGCAGGACATGCTGACCCCTGCAGATGA
TCCAGCTCATGGACGTCTGTGGAAGCAGGAGGGTGGACCTGAGGGAGGCCCTGGATCGAGCATTGAGG
AGTCACCCCTCTCTGTGCTGGCTATTGTGTCGCCACATATGTCGGGATGGCGATGGCACAGCGACA
ACATCATGATCCGAGAGAGTGGCAGCTGTTCCACATTGATTGGCCACTTCTGGGAATTCAAGACCA
AGTTTGGAAATCAACCGCAGCGTGTCCCATTCACTCCTCACCTACGACTTTGCCATGTGATTCAAGGG
AGACTAATAATAGTGAGAAATTGAACGGTTCCGGGACTAGTGTGAAAGGGCTACACCATCCTGCCGCC
ACGGGCTCTCTCCACCTTTGCCCTGATGCCGGCAGGCCCTGAGCTAGCTGCTCCAAAG
ACATCCAGTATCTCAAGGACTCCCTGGCACTGGGAAACAGAGGAGGAGGACTGAAGCACTTCCAGTGA
AGTTAACGAAGCCCTCCGTGAGAGCTGGAAACAAAGTGAACGGCTGCCACACGTGTCAAAGACA
ACAGGCAGTAG

(Double underline indicates bases bordering the splice junction)

TABLE 5

PIK3CD variant 3 (lacking exon 10 and exon 23)
Nucleotide Sequence (2877 nt, SEQ ID No. 14):

ATGCCCTGGGGACTGCCCATGGAATTCTGGACCAAGGAGGAGAATCAGAGCTGTGGTTGACT
TCTGCTGCCACAGGGCTACCTGAACTTCCCTGTGTCGCCATGCCAACCTCAGCACCATCAAGCA
GCTGCTGTGGCACCGGCCAGTATGAGGCCCTCTCCACATGCTCAGTGGCCCCAGGCCCTATGTGTT
ACCTGCATCAACCAAGACAGCGGAGCAGCAAGAGCTGGAGGAGGAGCAACGGCTGTGACGTGCAGC
CCTTCCCTGCCGTCGCGCTGGTGGCCGTGAGGGCAGCGCTGAAGAAGCTCATCAACTCACAGAT
CAGCCTCCTCATCGCAAAGGCCCTCACGAGTTGACTCCTGTGCAACCGAGAAGTGAACGACTTCGC
GCCAAGATGTGCAATTCTGCGAGGAGGCCCTGGCTCAAACCTGGGGCTGGTACCCGTGGCTCCGAA
AGTACAGTTCCCCCTGCAGCTGGAGGCCCTGGCTCAAACCTGGGGCTGGTACCCGTGGCTCCGAA
CCGGGCTCTGGTCAACGTTAAGTTGAGGGCAGCGAGGAGGAGCTCACCTCCAGGTGTCCACCAAG
GACGTGCCGCTGGCCTGATGCCCTGCGGAAGAAGGCCACAGTGTCCGGCAGCCGTGGTGG
AGCAGCCGGAAGACTACACGCTGCAGGTGAACGGCAGGCATGAGTACCTGTATGGCAGCTACCCGCTCG

TABLE 5 -continued

PIK3CD variant 3 (lacking exon 10 and exon 23)
Nucleotide Sequence (2877 nt, SEQ ID No. 14):

CCAGTTCCAGTACATCTGCAGCTGCCCTGCACAGTGGGTTGACCCCTCACCTGACCATGGTCATTCCCTCC
TCCATCCTCGCCATGCCGGATGAGCAGAGCAACCCCTGCCCTCAGGTCCAGAAACCGCGTGCAAAC
CTCCCATTCCTGCGAAGAAGCTGGTGGTGAGGCCGGCTTTCCACGGAACGAGATGCTGTGAAAGACGG
TGTCCAGCTCGGAGGTGAGCGTGTGCTCGAGCCGTGTGAAGCAGCGGCTGGAGTTGACATCAACATCT
GGACACTGCCCGCATGGCCGCTCTGCTTGCCTGATGCCGTGATCGAGAAAGCCAAGAAGGCTCGCT
CCACCAAGAAGAAGTCCAAGAAGGCGACTGCCCATGCCCTGGCCAACCTCATGCTGTTGACTACAAGG
ACCAGCTTAAGACCGGGAAACGCTGCCCTACATGTGGCCCTCCAGATGAGAAGGGGAGCTGCTGA
ACCCCCACGGGCACTGTGCGCAGTAACCCCAACACGGATAGGCCGTGCCCTGCTCATCTGCCCTGCCGAGG
TGGCCCGCACCCCGTGTACTACCCGCCCTGGAGAAGATCTGGAGCTGGGGGAGACACAGCAGTGTG
ATGTCAACGAGGAGGAGCAGCTGCAGCTGCCGAAATCCTGGAGCGGGGGCTGGGGAGCTGTATGAGC
ACGAGAAGGACCTGGTGTGAAAGCTGCCATGAAGTCCAGGAGCACTCCGGAGGCCTAGCCCGCTGC
TGCTGGTCACCAAGTGGAAACAGCATGAGGATGTGGCCAGATGCTTACCTGCTGTGCTCCCTGCCGAGC
TGCCCGTCTGAGGCCCTGGAGCTGCTAGACTTCAGCTCCCGATTGCCACGTAGGCTCTTGCCATCA
AGTCGCTGCCGAAACTGACGGAGATGAGCTGTTCCAGTACCTGCTGCAGCTGGTGCAGGTGCTCAAGTACG
AGTCCTACCTGGACTGCCGAGCTGACCAATTCTGCTGGACCCGGCCCTGCCAACCGCAAGATGCCACT
TCCTTTCTGGCACCTCCGCTCGAGATGCACGTGCCGTGGCTGCCCTGCCCTGGCCATCTGGAGG
CCTACTGCAGGGCAGCACCCACCATGAAGGTGCTGATGAAGCAGGGGAGCACTGAGCAAACGTGAAGG
CCCTGAATGACTCGTCAGCTGAGCTCTCAGAAGACCCCAAGCCCCAGACCAAGGAGCTGACTTGT
GCATGCCGAGGAGGCTACCTAGAGGCCCTCCCCACCTGCAGTCCCCACTGCCACCCAGCACCTGCTGG
CTGAAGTCTGCCGAGCAGTGCACCTCATGGACTCCAAGATGAAGCCCCCTGTGGATCATGTACAGCAACG
AGGAGGCAGGCAGCGGGCAGCGTGGCATCATCTTAAGAACGGGATGACCTCCGGCAGGACATGCTGA
CCCTGCAGATGATCCAGCTCATGGACGTCTGTGAAAGCAGGAGGGCTGGACCTGAGGGAGGCCCTGG
GAGCCATTGAGGAGTTACCCCTCCTGTGCTGGCTATTGTGTGGCACATATGTCTGGCATTGGCGATC
GGCACAGCGACAACATCATGATCCGAGAGAGTGGCAGCTGTTCCACATTGATTTGGCACTTCTGGGG
ATTCAGAACCAAGTTGAACTAACCGCGAGCGTGTCCCATCTCACCTGACTTTGTCCATGTGA
TTCAAGCAGGGGAGACTAATAATAGTGAAGAAATTGAACGGTCCGGCTACTGTGAAAGGGCCTACACCA
TCCTGCCGCCACGGCTCTCTCCACCTTTGCCCTGATGCCGGCAGGCCTGCCAGCTCA
GCTGCTCCAAAGACATCCAGTATCTCAAGGACTCCCTGGCAGTGGGAAAACAGAGGAGGAGGCACTGAAGC
ACTTCCGAGTGAAGTTAACGAAGCCCTCCGTGAGAGCTGGAAAACCAAGTGAACGGCTGCCAACACG
TGTCCAAGAACACAGGAGTAG

(Double underline indicates bases bordering the splice junction)

TABLE 6

PIK3CD variant 4 (with large deletion) Nucleotide
Sequence (1836 nt, SEQ ID No. 16):

ATGCCCTGGGTGGACTGCCCATGGAATTCTGGACCAAGGAGGAATCAGAGCTGGTGGTTGACT
TCTGCTGCCACAGGGTCTACCTGAACCTCCCTGTGCCCCAATGCCAACCTCAGCACCATCAAGCA

TABLE 6 -continued

PIK3CD variant 4 (with large deletion) Nucleotide Sequence (1836 nt, SEQ ID No. 16):

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GCTGCTGTGGCACCGGCCAGTATGAGCCCTCTTCCACATGCTCAGTGCCCCAGGCTATGTGTC
ACCTGCATCAACCAGACAGCGGAGCAGCAAGAGCTGGAGGACAGCAACGGCGTCTGTGACGTGAGC
CCTTCCTGCCGCTCTGCGCTGGTGGCCGTGAGGGCGACCGCGTGAAGAAGCTCATCAACTCACAGAT
CAGCCTCCTCATCGCAAAGGCCCTCACGAGTTGACTCCTTGTGCGACCCAGAAGTGAACGACTTCGC
GCCAAGATGTGCCAATTCTCGAGGGAGGCGCCGCCGGCAGCAGCTGGCTGGGAGGCTGGCTGC
AGTACAGTTCCCCCTGAGCTGGAGCCCTGGCTAAACCTGGGGCTGGTACCCCTGCGGCTCCGAA
CCGGGCCCTCTGGTCAACGTTAACGTTGAGGGCAGCGAGGAGAGCTTCACCTTCAGGTGTCACCAAG
GACGTGCCGCTGGCGCTGATGCCCTGCGGAAGAAGGCCACAGTGTCCGGCAGCCGCTGGTGG
AGCAGGCCGAAGACTACACGCTGCAGGTGAACGGCAGGATGAGTACCTGATGGCAGCTACCGCTCG
CCAGTCCAGTACATCTGCAGCTGCCTGCACAGTGGTTGACCCCTCACCTGACCATGGTCCATTCTCC
TCCATCCTCGCCATGCCGAGAGCACCCCTGCCCGCAGGTCCAGAAACCGCGTGCCTAAACAC
CTCCCATTCTCGCGAAGAAGCCTTCTCTGTGTCCTGTGGTCCCTGGAGCAGCGTTCCGATCGAGCT
CATCCAGGGCAGCAAAGTGAACGCCGACGAGCGGATGAAGCTGGTGTGCAGGCCGGCTTCCACGGC
AACGAGATGCTGTGCAAGACGGTGTCCAGCTGGAGGTGAGCGTGTGCTGGAGCCGTGTGAAAGCAGC
GGCTGGAGTTGACATCACATCTGCACCTGCCCGCATGGCCGCTCTGCTTGGCCTGTACGCCGT
GATCGAGAAAGCCAAGAAGGCTGCTCCACCAAGAAGAAGTCCAAGAAGGCCACTGCCCTTG
GCCAACCTCATGCTGTTGACTACAAGGACAGCTTAAGACGGGGAACGCTGCCTACATGTGGCCCTC
TCCGTGCTGGTATTGTTGAGCTGTCACATATGCTGGCATTGGGATCGGCACAGCGACAAACATCATGATC
CGAGAGAGTGGGAGCTGTCACATTGATTTGGCACTTCTGGGAATTCAAGACCAAGTTGGAATC
AACCGCGAGCGTGTCCATTCTCACCTACGACTTGTCCATGTGATTCAAGGGGAAGACTAATAAT
AGTGAGAAATTGAGCGTCCGGGACTGTGAAAGGGCTACACCACCTGCGGCCACGGCTTCTC
TTCCTCCACCTCTTGCCCTGAGGGGGGGCAGGCTGAGCTCAGCTGCTCAAAGACATCCAGTAT
CTCAAGGACTCCCTGGCACTGGGAAACAGAGGAGGAGGACTGAAGCACTCCGAGTGAAGTTAACGAA
GCCCTCCGTGAGAGCTGGAAAACCAAAAGTGAACCTGGCTGGCCACACGTGTCCTAAAGACAAACAGGCA
TAG

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(Double underline indicates bases bordering the deletion junction)

TABLE 7

Primers for detecting PIK3CD variants

Primer across the junction between PIK3CD exon 9 and 11 (SEQ ID No. 6)	<u>TGCGAAGAAGCTGGTGGTGC</u>
Primer sequences across the junct. between PIK3CD exon 22 and 24 (SEQ ID No. 10)	<u>TGGACCTGAGGGAGGCCCT</u>
Primer sequences across the deleted region (nt1329-2627) of PIK3CD (SEQ ID No. 15) :	<u>ACATGTGGCCCTCTCCTG</u>

TABLE 8

sirRNA for selectively knockdown PIK3CD full length and variants expression

50	sirRNA targeting PIK3CD exon 23 (siPIK3CD-ex23)
Sense (SEQ ID No. 4) : 5' CCAACAUCCAACUCAACAA <u>dTdT</u> 3'	
55	Antisense (SEQ ID No. 5) : 3' dTdTGGUUGUAGGUUGAGUU-GUU (5'-P) 5'
60	sirRNA targeting junction spanning between exon 9 and exon 11
Sense (SEQ ID No. 8) 5' CUGCGAAGA <u>AGCUGGUGGUdTdT</u> 3'	
65	Antisense (SEQ ID No. 9) 3' dTdTGACGCUUCUUC <u>CGACAC-CA</u> (5'-P) 5'

(Double underline indicates bases bordering the splice junction)

TABLE 8-continued

siRNA for selectively knockdown PIK3CD full length and variants expression
siRNA targeting junction spanning between PIK3CD exon22 and exon 24 (siPIK3CD-S)
Sense (SEQ ID No. 12) 5' <u>UGAGGGAGGCCU</u> GAUCGAdTdT 3'
Antisense (SEQ ID No. 13) 3' dTdTAC <u>UCCCUC</u> CGGGACCU-AGCU (5'-P)5'
siRNA targeting junction spanning the deleted sequences of PIK3CD variant 4
Sense (SEQ ID No. 17) 5' <u>CCUCUCCUGUGCUGG</u> CUAudTdT 3'
Antisense (SEQ ID No. 18) 3' dTdT <u>GAGAGGACACGACCG-AUA</u> (5'-P)5'

(Double underline indicates bases bordering the splice junction)

TABLE 9

FGFR3 (Full length) Nucleotide Sequence (2421 nt, SEQ ID No. 19)
ATGGGCCCCCTGCCTGCGCCCTCGCGCTCTCGTGGCGTGGCCATCGT
GGCCGGCGCCTCCCTCGAGTCCTTGGGGACGGAGCAGCGCGTGTGGGC
GAGCGGCAGAAGTCCCGGGCCAGAGCCGCCAGCAGGAGCAGTGGTC
TTCGGCAGCGGGATGCTGTGGAGCTGAGCTGTCCCCGCCGGGGTGG
TCCCATGGGCCACTGTCTGGTCAAGGATGGCACAGGGCTGGTCCCCT
CGGAGCGTGTCTGGGGCCACGGGCTGAGGTGCTGAATGCCCTCC
CACGAGGACTCCGGGCCTACAGCTGCCGGCAGCGCTCACCGAGCGT
ACTGTGCCACTTCAGTGTGCCGGTGACAGACGCTCCATCCTGGAGATG
ACGAAGACGGGAGGACGAGGTGAGGACACAGGTGTGGACACAGGGCC
CCTTACTGGACACGGCCGAGGGATGGACAAGAAGCTGCTGCCGTGCC
GGCGCCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTC
CCTCCATCTCTGGCTGAAGAACGGCAGGGAGTTCCGCCGGCAGCACCGC
ATTGGAGGCATCAAGCTGCCATCAGCAGTGGAGCCTGGTATGGAAAG
CGTGGTCCCCCTGGACCGCGGAAACTACACCTGCGTCGTGGAGAACAGT
TTGGCAGCATCCGGCAGACGTACACGCTGGACGTGCTGGAGCGCTCCCG
CACCGGGCCATCTGCAGGCGGGCTGCCGCCAACAGAGCGCGGTGCT
GGGCAGCGACGTGGAGTCCACTGCAAGGTGTACAGTGACGCACAGCCCC
ACATCCAGTGGCTCAAGCACGTGGAGGTGAATGGCAGCAAGGTGGCCCG
GACGGCACACCTACGTTACCGTGTCAAGACGGCGGGGCTAACACCAC
CGACAAGGAGCTAGAGGTCTCTCCTTGCAACACGTCACCTTGAGGACG
CCGGGGAGTACACCTGCCCTGGCGGCAATTCTATTGGTTTCTCATCAC
TCTGCGTGGCTGGTGTGCTGCCAGCCGAGGGAGCTGGTGGAGGCTGA
CGAGGGGGCAGTGTGTATGCAGGCATCCTCAGCTACGGGTTGGCTCT
TCCCTGTTCATCTGGTGTGGCGGCTGTGACGCTTGCCGCTGCCGAGC
CCCCCAAGAAAGGCCCTGGCTCCCCCACCGTGCACAAGATCTCCGCTT

TABLE 9-continued

FGFR3 (Full length) Nucleotide Sequence (2421 nt, SEQ ID No. 19)
5 CCGCTCAAGCGACAGGTGCTCCCTGGAGTCAAACGCCATGAGCTCA
ACACACCACCTGGTGCATCGAAGGCTGCTCAGGGAGGGCCCCACG
CTGGCCAATGTCTCCGAGCTCGAGCTGCCGACCCAAATGGGAGCT
10 GTCTGGGCCCCGCTGACCTGGCAAGCCCCTGGGAGGGCTGCTTCG
GCCAGGTGGTATGGGGAGGCCATGGCATTGACAAGGACCGGGCCGC
AAGCTGTCAACCGTAGCGTGAAGATGCTGAAAGACGATGCCACTGAA
15 GGACCTGCGACCTGGTCTGAGATGGAGATGATGAAGATGATCGGGA
AACACAAAAACATCATCAACCTGCTGGCGCCTGCACGCAGGGCGGCC
CTGTACCGTCTGGGGAGTACCGGCCAAGGTAACCTGCCGGAGTTCT
20 GCGGGCGCGGCCGGCCCTGGACTACTCTTCGACACCTGCAAGC
CGCCCGAGGAGCAGCTACCTCAAGGACCTGGTGTCTGCCCTACCA
GTGGCCGGGGATGGAGTACTGGCTCCCAGAAGTGCATCCACAGGG
25 CCTGGCTCCGCAATGTGCTGGTACCGAGGACAACGTGATGAAGATCG
CAGACTTCCGGCTGGCCGGAGCTGACACACTGACTACTAACAGAAG
ACGACCAACGGCGGCTGCCGTGAAGTGGATGGCGCCTGAGGCCTTGT
30 TGACCGAGTCTACACTCACAGAGTGAAGTCTGGTCTTGGGTCTGC
TCTGGGAGATCTTCACGCTGGGGCTCCCGTACCCGGCATCCCTGTG
GAGGAGCTTCAAGCTGCTGAAGGAGGGCACCGCATGGACAAGCCGC
35 CAACTGCACACAGACCTGACATGATCATGCCGGAGTGCTGGCATCCG
CGCCCTCCAGAGGCCACCTCAAGCAGCTGGTGGAGGACCTGGACCGT
GTCCTTACCGTACGCTCCACCGACGAGTACCTGACCTGTCGCCCTT
CGAGCAGTACTCCCCGGTGGCCAGGACACCCCACTCCAGCTCCTCAG
40 GGGACGACTCCGTGTTGCCACGACCTGCTGCCCGGCCACCCAGC
AGTGGGGCTCGCGGACGTGA
(Exon 14 is indicated by double underline. Primers useful for detection of exon 14 splicing variants are underlined.)
45

TABLE 10

FGFR3 variant 1 (lacking exon 14) Nucleotide Sequence (2298 nt, SEQ ID No. 25):
50 ATGGGCCCCCTGCCTGCGCCCTCGCGCTCTCGTGGCGCTGGCCATCGT
GGCCGGCGCTCCCTGGAGTCCTGGGGACGGAGCAGCGCGTGTGGGC
GAGCGGAGAAGTCCGGCCAGAGCCGGCAGCAGGAGCAGTGGTC
55 TTGGCAGCGGGATGCTGTGGAGCTGAGCTGCCCCGCCGGGGTGG
TCCCATGGGCCACTGTCTGGTCAAGGATGGCACAGGGCTGGTGCCT
CGGAGCGTGTCTGGGGGCCAGCGGCTGCAGGTGCTGAATGCCCTC
60 CACGAGGACTCCGGGCCTACAGCTGCCGGCAGCGGCTCACGAGCGCGT
ACTGTGCCACTTCAGTGTGCCGGTACAGACGCTCACCTCGGGAGATG
ACGAAGACGGGAGGACGAGGTGAGGACACAGGTGTGGACACAGGG
65 CCTTACTGGACACGGCCGAGCGGATGGACAAGAGCTGCTGCCGTGCC

23

TABLE 10-continued

FGFR3 variant 1 (lacking exon 14) Nucleotide Sequence (2298 nt, SEQ ID No. 25):
GGCGGCCAACACCGTCGGCTTCCGCTGCCAGCCAGCGTGGCAACCCACTC
CCTCCATCTCCTGGCTGAAGAACGGCAGGGAGTTCCCGCGCGAGCACCGC
ATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGGTCATGGAAAG
CGTGGTGCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAGT
TTGGCAGCATCCGGCAGACGTACACGCTGGACGTGGAGCGCTCCCG
CACCGGCCCATCTGCAGGGGGCTGCCGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCC
ACATCCAGTGGCTCAAGCACGTGGAGGTGAATGGCAGCAAGGTGGCCCG
GACGGCACACCCATCGTTACCGTGTCAAGACGGCGGGCGTAACACCAC
CGACAAGGAGCTAGAGGTTCTCCTTGCAACACGTACCTTGAGGACG
CCGGGGAGTACACCTGCTGGGGCAATTCTATTGGTTTCTCATCAC
TCTGCGTGGCTGGTGTGCTGCCAGCCAGGGAGCTGGTGGAGGCTGA
CGAGGCGGGCAGTGTGTATGCAGGCATCCTCAGCTACGGGGTGGCTTCT
TCCTGTTCATCTGGTGGTGGGGCTGTGACGCTCTGCCCTGCCAGC
CCCCCAAAGAAGGCTGGCTCCCCCACCGTGCACAAGATCTCCGCTT
CCCGCTCAAGCGACAGGTGTCCCTGGAGTCCAACCGCTCATGAGCTCCA
ACACACCACGTGGCGCATCGAAGGCTGTCTCAGGGGAGGGCCCACG
CTGGCCAATGTCTCGAGCTCGAGCTGCCCGACCCAAATGGGAGCT
GTCTCGGGCCCGGCTGACCTGGCAAGGCCCCCTGGGGAGGGCTGCTCG
GCCAGGTGGTATGGCGGAGGCATCGCATTGACAAGGACGGGGCGCC
AAGCCTGTCACCGTAGCCGTGAAGATGCTGAAAGACGATGCCACTGACAA
GGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGATCGGA
AACACAAAAACATCATCAACCTGCTGGCGCTGACCGCAGGGCGGGCC
CTGTACGTGCTGGAGTACCGGCCAGGGTAACCTGCGGGAGTTCT
GGGGCGCGGCCGCCGGCTGGACTACTCCCTCGACACCTGCAAGC
CGCCCGAGGAGCAGCTCACCTCAAGGACCTGGTGTCTGCGCTACCAG
GTGGCCCGGGCATGGAGTACTGGCTCCCGAAGGGCCGGCTGCCGT
GAAGTGGATGGCCCTGAGGCCTGTTGACCGAGTCTACACTCACCAGA
GTGACGTCTGGCTTTGGGTCTGCTCTGGAGATCTTACCGCTGGGG

24

TABLE 10-continued

FGFR3 variant 1 (lacking exon 14) Nucleotide Sequence (2298 nt, SEQ ID No. 25):
GGCTCCCGTACCCGGCATCCCTGTGGAGGAGCTTCAAGCTGCTGAA
GGAGGGGCCACCGCATGGACAAGCCGCCAACTGCACACACGACCTGTACA
TGATCATCGGGAGTGTGGCATGCCGCCCTCCAGAGGCCACCTTC
10 AAGCAGCTGGTGGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGA
CGAGTACCTGGACCTGTGGCGCTTCGAGCAGTACTCCCCGGTGGCC
15 AGGACACCCCCAGCTCAGCTCAGGGGACGACTCCGTGTTGCCAC
GACCTGCTGCCCGGGCCACCCAGCAGTGGGGCTCGCGACGTGA

(Double underline indicates bases bordering the splice junction)

20

TABLE 11

Primer across the junction between FGFR3 exon 13 and 15
<u>TTGGCCTCCCAGAACGGCCGGCT</u>

(Double underline indicates bases bordering the splice junction)

30

TABLE 12

siRNA for selectively knockdown FGFR3 full length and variants expression
<u>sirNA targeting FGFR3 exon 14:</u>
Sense (SEQ ID No. 22) 5' CUCGACUACUACAAGAAGAdTdT 3'
40 Antisense (SEQ ID No. 23) 3' dTdTGAGCUGAUGAUUCU-UCU (5'-P) 5'
siRNA targeting splice junction between FGFR3 exon 13 and 15
<u>sirNA targeting FGFR3 exon 13:</u>
Sense (SEQ ID No. 26) 5' CCUCCCAGAACGGCCGGCU dTdT 3'
45 Antisense (SEQ ID No. 27) 3' dTdTGGAGGGCUU <u>CCCCGC</u> -CGA (5'-P) 5'

(Double underline indicates bases bordering the splice junction)

TABLE 13

TSC2 (full length) Nucleotide Sequence (5424 nt, SEQ ID No. 28)

ATGGCCAAACCAACAAGCAAAGATTCAAGGCTTGAAGGAGAAGTTAACGATTCTGTGGAGCTGGGAACACCG
AGGCCAAATCCAGGTCTGCAGAGGTAACAGACGGAGTTTACATCACCGCGGAAATACTGAGAGAACCTG
AGCATGGAATGTGGCTCAACAATCGCATTGGATGATAGGGCAGATTGTGAAGTCGAAAACCAAGAAA
TTTGAAGAGCACGCAGTGGAAAGCACTCTGGAAGGCCTCGCGGATCTGTGAGCCGGAGCGCCGCTGGAG
GCCCGCCACCGGGTCTGGCTCTGCTGAAGGCCATCGCAGGGGAGCGCTTGGGGTCCTCAGA
GCCCTCTTAAAGTCATCAAGGATTACCCCTCAACGAAGACCTCACGAAAGGCTGGAGGTTTCAAG
GCCCTCACAGACAATGGGAGACACATCACCTACTTGGAGGAAGAGCTGGCTGACTTGTCTGCAGTGGATG

TABLE 13-continued

TSC2 (full length) Nucleotide Sequence (5424 nt, SEQ ID No. 28)

GATGTTGGCTTGTCCCTCGGAATTCTTCTGGTGCTGGTGAACCTGGTCAAATTCAATAGCTGTTACCTCGAC
 GAGTACATCGCAAGGATGGTTCAGATGATCTGCTGTGCGTCCGGACCGCGTCTCTGGACATAGAG
 GTCTCCCTGCAGGTGCTGGACGCCGTGGTCTGCTACAACACTGCCCTGCCGGCTGAGAGCCTCCCGCTGTTCATC
 GTTACCCCTCTGTCGACCATCAACGTCAGGGAGCTCTGCGAGCCTGCTGGAGCTGATGCGAACCTCCTT
 GGCACCCACCTGGGCCACAGGCCATCTAACACATGTGCCACCTATGGAGGACAGAGCCTACATGGAGGAC
 CGCCGCCCTGCTGAGAGGAGCGCTGTTTTGTGGCATGGCTCTGGGGAGCCCACCGGCTTATTCTC
 AGGAACTCGCCACATCTGTGTTGCCATCATTACCAGGCCATGGCATGTCGAACGAGGTGGTGTCTTAT
 GAGATCGTCCTGTCCATCACCAGGCTCATCAAGAAGTATAGGAAGGAGCTCCAGGTGGCTGGACATT
 CTGCTGAACATCATCGAACGCCCTTCAGCAGCTCCAGACCTTGACAGCCGGAGCTCAGGACCATCGTC
 CATGACCTGTTGACCACGGTGGAGGAGCTGTGACCAGAACAGAGTTCCACGGGCTCAGGAGAGATACTT
 GAACGGTGGAGAGATGTGCGGACCAAGGGCTGAGTCCTCCCTCTGAACCTGATCTCTATAGAGCGCAG
 TCCATCCACCCGCCAAGGACGGCTGGATTCAAGAACCTGCAGCGCTGATGGAGAGATTCTTCAGGAGCGAG
 TCCCGAGGCGCCGTGCGCATCAAGGTGCTGGACGTGCTGTCCTTGTGCTCATCAACAGGCAGTTCTAT
 GAGGAGGAGCTGATTAACTCAGTGGTCACTCGCAGCTCTCCACATCCCCGAGGATAAAAGACCACCGAGTC
 CGAAAGCTGGCACCCAGTTGCTGGTGACCTGGCAGAGGGCTGAGCACACACCCACTTCACAGCCTGCTG
 GACATCATCGAGAAGGTGATGGCCCGCTCCCTCTCCCCACCCCGAGCTGGAAGAAAGGGATGTGGCGCA
 TACTCGGCTCCCTGGAGGATGTGAGACAGCCGCTGGTGTGAGATGCTGGTCAAGCACATTCAAGCTGTAC
 ACCCTGCGCTGCAAGGCCACGCCACCGCTGTGAGATGCTGGTCAAGCACATTCAAGCTCCACTACAAGCAC
 AGCTACACCCGCCAACCGAGCAGCATCGGCTGCAAGGCC**TTTGACTTCTGTTGCTGCTGCGCTGGGCCGAC**
 TCACTGCACCGCCTGGCCTGCCAACAAAGGATGGAGTCGTGCGGTTCAAGCCCTACTGCGCTGCGACTAC
 ATGGAGGCCAGAGAGAGCTCTGAGAAGAACAGCCAGCGGCCCTTCTCCCTCCACAGGGCTCTGGCCCG
 GCCCTGCAGGCCCCCGTGGGCTGGGTCCTGCCCCACTCCCTGCTCTCCCGTCTGCTGAGTGC
TTGAAGCAGGAGCTCTGACTGGAAGGTGCTGAAGCTGGTCTGGCAGGCTGCCTGAGTCCCTGCGTATAAA
GTGCTCATCTTACTTCCCTGCACTGTGACAGCTGCTGCTCTGCTCTGCTCATGCTTCAGGCCA
 AAAGACACTGGAGCGGCTCCGAGGCGCCCAAAGGCTCTCCAGAACACTGACTTCACCTGGCTGGTTCCA
 GTGCTGACAGCATTAATCTTACCATAAACTACCTGGACAAAACAAACAGCGCGAGATGGTCTACTGCGCTG
 GAGCAGGCCCTATCCACCGCTGTGCCAGCGCTGCGCTGGCCATCTGAGCGTGGAGATGCCT
 GACATCATCATCAAGGCCTGCCCTGGTGTGAGCTACGCACATCTCAGCCACAGCCAGCATGGCC
 GTCCCACTGCTGGAGTTCTGTCACCTGCCAGGCTGCCACCTCTACAGGAACCTTGCCGGAGCAG
 TAGCCAGTGTGTTGCCATCTCCCTGCCGTACACCAACCCCTCAAGTTAATCAGTACATCGTGTCTG
 GCCCATCACGTCATAGCCATGTGGTTCATCAGGTGCCCTGCCCTCCGAAGGATTTGCCCCCTTCATC
 ACTAAGGGCCTCGGGCCAATGTCCTTGTCTTTGATGACACCCCCGAGAAGGACAGCTTCAGGGCCGG
 AGTACTAGTCTCAACAGAGAGACCAAGAGCTGAGGATAGCCAGACCCCAAACAAGGCTTGAATAACTCT
 CCACCCGTGAAAGAATTCAAGGAGAGCTCTGCAGCCAGGCCCTCCGGTGCCGAGCATCAGTGTCTGAA
 CATGTGGTCCCGCAGCAGGATAACAGACGTCCTCACCAGTGCAGCTGGGCTCTGAGATGAGAAGACTCGT
 GCCCAGGCTGACGATAGCCTGAAAAACCTCCACCTGGAGCTCACGGAAACCTGTCTGGACATGATGGCTCGA
 TACGTCTCTCCAACCTCACGGCTGCCCCGAAGGGTCTCTGTGGCGAGTCCCTCTAGCGGGTGGCAGG
 ACCAAAACCTGGCTGGTTGGGACAAGCTTGTCACTGTGACGACAAGCGTGGAAACCGGGACCGGTGTTA
 CTAGGCCTGGACTCGGGGAGCTGCAGTCCGGCCGGAGTCAGCTCCAGCCCCGGGTGCTGAGACAG

TABLE 13-continued

TSC2 (full length) Nucleotide Sequence (5424 nt, SEQ ID No. 28)

ACCAAGGAGGCCGGCCAAGCTGGAGTCCCAGGTGGCAGCAGGTGTCCCGTGGGCCCGGGATCGGGTC
 CGTTCCATGTCGGGGGCCATTGGCTTCGAGTTGGCCCTGGACGTGCCGCCCTCCAGTTCTGGCAGT
 GCCACTTCTCCAGGACCACGGACTGCACCAGCCGAAACCTGAGAAGGCCTCAGCTGGCACCCGGTTCC
 GTGCAGGAGAACAGACAACTGGCGCTATGTGCCCTGCTGACCCAGGGCTGGCGAGATCCTGGTCC
 AGGCCAACAGGAACACCAGCTGGCTGATGAGCCTGGAGAACCCGCTCAGCCCTTCTCCTCGGACATCA
 AACATGCCCTGCAGGAGCTGCTAACGCCCTCATGGCGCTGAGCGCTTAAGGAGCACGGGACACAGCC
 CTGTACAAGTCACTGTCGGTGCCGGCAGGCCAGCGCAAACCCCCCTCCTCGCCTCGCTCAAACACAGTG
 GCCTCTTCTCCTCCCTGTACCAGTCCAGCTGCCAAGGACAGCTGCACAGGAGCTTCCCTGGCAGACTCC
 GCGTGGTCATGGAGGAGGAAGTCGGGCGAGGTTCTGTGCTGGTGGAGCCCCAGGGTGGAGGACGTT
 GAGGCAGCGTAGGCATGGACAGGCGCACGGATGCCCTACAGCAGGTCGCTCAGTCTCCAGCCAGGAGGAG
 AAGTCGCTCCACGCGGAGGAGCTGGTGGCAGGGCATCCCCATGAGCAGTCGCTCCTCGGAGGGTGGC
 CGGCCCTCTGGACCTCTCCTCCAGCCCTCGCAGCCCTGAGCAAGTCCAGCTCCTCTCCGAGCTGCAG
 ACTCTGCAGGACATCCTCGGGACCCCTGGGACAAGGCGACGTGGCCCTCGGCGAAGACAGTCGGGCCAG
 CGGTACAGTCAGGGACCCCTGGACGGGAAAGTGCTGCCCTGGCCCTCGGCGAAGACAGTCGGGCCAG
 CCCGAGGGTCCCTGCCTCCAGCTCCCCCGCTGCCAGTGGCTCCGGCCAGGGTTACACCATCTCC
 GACTCGGCCCATCACGCAAGGGCAAGAGAGTAGAGAGGGACGCCCTAAAGAGCAGAGCCACAGCCTCA
 GCAGAGAAAGTCCAGGCATCAACCCAGTTCTGTGCTGCCATGAGTCAGTCCTTGAGCGGTCGGTGAG
 GAGTCAAACAAGCCAATCCTGCTGCCAATGAGTCAGTCCTTGAGCGGTCGGTGAGCTCCTCGACCAG
 ATCCCATCATAGCACACCCACAAGATGCCCTGTATGTTGGAGAAGGCCAGAGCAACAGCAGCTGCC
 ATCTGTCCAATGAGCATGGCTCTACAGGTACACGGAGTTCTGACGGGCTGGCCGGCTCATCGAGCTG
 AAGGACTGCCAGGCCACAAGGTGACCTGGAGGCTGGACGTGTGGTGAGGACGGCAGTTACACCTAC
 TCGCTGGCACGATGACATCATGCAAGCCGCTTCCACATGCCACCCGATGCCACCAAGGACGTGGACAAG
 CACCGCTGCGACAAGAAGGCCACCGACTGGCACGACTTGTGCTTACATGACTCCGGTGAGGAC
 TTCAAGCTTGGCACCATCAAGGGCAGTTCAACTTGTCCACGTGATGTCACCCGCTGGACTACGAGTG
 AACCTGGTGTCCCTGCAGTGAGGAAAGACATGGAGGGCTTGTGGACACAGCGTGGCAAGATCGTGTCT
 GACCGAACCTGCCCTCGTGGCCCGCAGATGGCCCTGCACGCAAATATGGCCTCACAGGTGCATCATAGC
 CGCTCCAACCCACCGATACTACCCCTCCAAGTGGATTGCCGCTCGCCACATCAAGCGCTCCGCCAG
 CGGATCTGCGAGGAAGCCGCTACTCCAACCCAGCCTACCTCTGGTCACCCCTCGTCCATAGCAAAGCC
 CCTGCACAGACTCCAGCGAGCCCACACCTGGCTATGAGGTGGCAGCGGAAGGCCCTCATCTCGGT
 GAGGACTTCACCGAGTTGTGAG

(Exon 19 is indicated by double underline. Primers useful for detection of exon 19 splicing variants are underlined.)

TABLE 14

TSC2 variant 1 (lacking exon 19) Nucleotide Sequence
(5301 nt, SEQ ID No. 34)

ATGGCCAAACCAACAAGCAAAGATTCAAGGCTTGAAGGAGAAGTTAAAGATTCTGTGGACTGGGACACCCG
 AGGCCAAATCCAGGTCTGCAGAGGGTAAACAGACGGAGTTATCATCACCGGAAATACTGAGAGAACTG
 AGCATGGAATGTGGCTCAACAATCGCATCGGATGATAGGGCAGATTGTGAAGTCGCAAAACCAAGAAA
 TTGAAAGAGCACCGAGTGGAAAGCACTTGGAAAGGCCGCTCGCGGATCTGTCAGCCGGAGCGGCCGCTGGAG

TABLE 14 - continued

TSC2 variant 1 (lacking exon 19) Nucleotide Sequence (5301 nt, SEQ ID No. 34)	
GCCCGGCACGGGTCTGGCTCTGTAAGGCCATCGTGAGGGCAGGGCTGGGTCAGA	
GCCCTCTTAAAGGTCAAGGATTACCTTCAACGAAGAACCTCACGAAAGGCTGGGTTCAAG	
GCCCTACAGACAATGGGAGACACATCACCTACTGGAGGAAGAGCTGGCTGACTTGTCTGCAGTGGATG	
GATGTTGGCTTGTCTCGGAATTCTCTGGTCTGGTGAACCTGGTCAAATTCAATAGCTGTTACCTCGAC	
GAGTACATCGAAGGATGGTCAGATGATCTGCTGTGCGTCCGGACCGCGTCTGTGGACATAGAG	
GTCTCCCTGCAGGTGCTGGACGCCGGTCTGCTACAACCTGCCTGCCGTGAGAGCCTCCGCTGTTCATC	
GTTACCCCTGTGCGACCATAACGTCAAGGAGCTGCGAGCCTGCTGGAGCTGATGCGAACCTCCTT	
GGCACCCACCTGGGCCACAGGCCATCTACAAACATGTGCCACCTATGGAGGACAGAGCCTACATGGAGGAC	
GGCCCCCTGTGAGAGGAGCGTGTGTTGGCATGGCTCTGGGGAGCCACCGGCTTATTCTCTC	
AGGAACCTGCCACATCTGTGTTGACATCTTACAGGCCATGGCATGTCGAACGAGGTGGTGTCTAT	
GAGATCGTCCTGTCCATCACCAGGCTCATCAAGAAGTATAGGAAGGAGCTCAGGTGGTGGCGTGGACATT	
CTGCTGAACATCATCGAACGGCTCTTCAAGCAGCTCCAGACCTTGGACAGCCGGAGCTAGGACCATCGTC	
CATGACCTGTTGACCACGGTGGAGGAGCTGTGACAGAGGAGTTCCACGGGTCAGGAGAGATACTTT	
GAACCTGGTGGAGAGATGTGCGGACCAAGGGCTGAGTCTCCCTCTGAACCTGATCTCTATAGAGCGCAG	
TCCATCCACCCGGCCAAGGACGGCTGGATTCAAGACCTGCAAGCGCTGATGGAGAGATTCTCAGGAGCGAG	
TCCCGAGGCGCCGTGCGCATCAAGGTGCTGGACGTGCTGTCCTTGCTGCTCATCAACAGCAGTTCTAT	
GAGGAGGAGCTGATTAACCTAGTGGTCATCTCGCAGCTCTCCACATCCCCAGGATAAAGACCAACAGGTC	
CGAAAGCTGGCACCCAGTTGCTGGTGACCTGGAGGGCTGCCACACACCACTTCAACAGCCTGCTG	
GACATCATCGAGAAGGTGATGGCCCCTCCCTCTCCCCACCCCGAGCTGGAAGAAAGGGATGTGGCGCA	
TACTCGGCTCCTGGAGGATGTGAAAGACAGCCGCTCTGGGCTTCTGGTCATCCTCAGACCAAGCTGTAC	
ACCCCTGCCTGCAAGCACGCCACGCGTGTGATGAGATGCTGGTCAAGCCACATTCAAGCTCCACTACAAGCAC	
ACCTACACCCGCCAATCGCAGCAGCATCCGCTGCCAGGCTTGAATTCTGTCCTGCTGCCGGCGAC	
TCACTGCACCCTGGCCTGGCCTGCCAACAAAGATGGAGTCGTCGGTCAAGCCCTACTGCGCTGCGACTAC	
ATGGAGCCAGAGAGAGGCTCTGAGAAGAAGACCAAGCGGCCCTTCTCCTCCCACAGGGCTCTGGCCG	
GGCGCTGCAGGCCCGCCGCGTGGGCTGGGCTGGCGCTACTCCCTGCTCTCCGCTGCTGAGTGC	
<u>TTGAAGCAGCTTCAGGCCAAAGACACTGGAGCGCTCGAGGCGCCAGAAGCTCTCAGAACTGAC</u>	
TTGCACCTGGCCGTGGTCCAGTGACAGCATTAACTCTTACATAACTACCTGGACAAAACCAAACAG	
CGCGAGATGGTACTGCCTGGAGCAGGGCTCATCCACCGCTGTGCCAGCCAGTGCCTGTCCTGT	
ATCTGCAGCGTGGAGATGCCTGACATCATCAAGCGCTGCCGTTCTGGTGGTGAAGCTCACGCACATC	
TCAGCCACAGCAGCATGGCGTCCACTGCTGGAGTTCTGCACTCTGCCAGGCTGCCACCTCTAC	
AGGAACCTTGCCGCGAGCAGTATGCCAGTGTGTTGCCATCTCCCTGCCACACCAACCCCTCAAGTT	
AATCAGTACATCGTGTCTGGCCCATCACGTCAAGCCATGTGGTCACTGGGTGACAGCTGCCCTGCC	
AAGGATTTGCTCTTCACTAAGGGCTGCCAATGCTCTTGTGTTGATGACACCCCGAG	
AAGGACAGCTCAGGCCCGGAGTACTAGTCACGAGAGACCAAGAGCTGAGGATGCCAGACCCCC	
AAACAAGGCTGAAATACTCCACCCGTAAAGAATTCAAGGAGAGCTGAGCCAGGCCCTCCGG	
CGCAGCATCAGTGTCTGAAACATGTGGCCGAGCAGGATAACAGACGTCCCTCACCGTGCAGCTGGGG	
TCTGAGATGAGAACTCCGTGGGCCAGGCTGACGATAGCCTGAAAAACCTCACCTGGAGCTACGGAAACC	
TGCTGGACATGATGGCTCGATACGCTTCTCAACTTCACGGCTGTCCGAAGAGGTCTCCTGTGGCGAG	
TTCCCTCTAGCGGGTGGCAGGACAAAACCTGGCTGGTGGAAACAAGCTGTCACTGTGACGACAAGCGT	

TABLE 14 - continued

TSC2 variant 1 (lacking exon 19) Nucleotide Sequence
(5301 nt, SEQ ID No. 34)

GGAACCGGGACCCGGTCGTTACTAGGCCTGGACTCGGGGGAGCTGCAGTCGGCCGGAGTCGAGCTCCAGC
CCCGGGGTGCATGTGAGACAGACCAAGGAGGCCGGCAAGCTGGAGTCCAGGCTGGCAGCAGGTGTCC
CGTGGGGCCCGGATCGGGTCCGTTCCATGTCGGGGGCCATGGTCTTCGAGTTGGCGCCCTGGACGTGCC
GCCTCCCAGTCTCTGGCAGTGCCACTTCTCCAGGACCACGGACTGCACCAGCCGCAAACCTGAGAAGGCC
TCAGCTGGCACCCGGTTCTGTGCAGGAGAAAGACGAACCTGGCGGCATGTGCCCTGCTGACCCAGGGC
TGGCGGAGATCTGGTCCGGAGGGCCACAGGGAAACACCAGCTGGCTGATGAGCCTGGAGAACCCGCTCAGC
CCTTCTCTCGGACATCAACAACATGCCCTGCAGGAGCTGCTAACGCCCTCATGGCGCTGAGCGCTTC
AAGGAGCACCGGGACACAGCCCTGTACAAGTCACTGTCGGTGCCGGCAGCCAGCACGGCAAACCCCTCCT
CTGCCCTCGCTCAAACACAGTGGCCTTTCTCTCCCTGTACAGTCCAGCTGCCAAGGACAGCTGACAGG
AGCGTTCTGGCAGACTCCGGCTGGTCATGGAGGAGGAAGTCCGGCGAGGTTCTGTGCTGGTGGAG
CCCCCAGGGTTGGAGGACGTTGAGGAGCGCTAGGCATGGACAGGCGCACGGATGCCCTACAGCAGGTGTCC
TCAGTCTCCAGCCAGGAGGAAGTCGCTCCACGCGGAGGAGCTGGTTGGCAGGGCATCCCCATCGAGCGA
GTCGTCCTCTGGAGGGTGCCGGCCCTCTGTGGACCTCTCCCTCGAGCCCTGAGCCCTGAGCAAGTCC
AGCTCCTCTCCGAGCTGCAGACTCTGCAGGACATCCTCGGGACCCCTGGGACAAGGCCGACGTGGCCGG
CTGAGCCCTGAGGTTAAGGCCGGTACAGTCAGGGACCCCTGGACGGGAAAGTGCTGCCTGGCTGGCCTCG
GGCGAACAGCTGGGCCAGCCGAGGGTCCCTGCCCTCCAGCTCCCCCGCTGCCAGTGGCTCCGG
CCCCGAGGTTACACCATCTCGACTCGGCCCACAGCAGGGCAAGAGAGTAGAGAGGGACGCCCTAAAG
AGCAGAGCCACAGCCTCAAATGCAGAGAAAGTGCAGGCATCAACCCAGTTCTGCTGAGTCACAGTCTTGA
GCGTCTCCCTGGAGGACTCGAGCTAAACAAAGCCAATCCTGCTGCCAATGAGTCACAGTCTTGA
TCGGTGAGCTCTCGACCAGATCCATCATCGACACCCACAAGATCGCGTCCTGTATGTTGGAGAAGGC
CAGAGCAACAGCGAGCTGCCATCCTGCAATGAGCATGGCTCACAGGTACGGAGTTCTGACGGC
CTGGGCCGGCTATCGAGCTGAAGGACTGCCAGCCGACAAGGTGTACCTGGAGGCCTGGACGTGTGGT
GAGGACGGCCAGTTCACCTACTGCTGGCACGATGACATCATGCAAGCCGTCTCCACATGCCACCGTATG
CCCCACCAAGGACGTGGACAAGCACCGCTGCGACAAGAAGGCCACCTGGCAACGACTTGTGTCATTG
TACAATGACTCCGGTGAGGACTCAAGCTGGCACCATCAAGGGCCAGTTCAACTTGTCCACGTGATCG
ACCCCGCTGGACTACGAGTGCAACCTGGTGTCCCTGCAGTGCAGGAAAGACATGGAGGGCTGTGGACACC
ACCGTGCCAAAGATCGTGTGACCGAACCTGCCCTCGAGTGCAGGAAAGACATGGCCCTGACCGAAATATG
GCCTCACAGGTGCATCATGCCCTCAACCCACCGATATCTACCCCTCAAGTGGATTGCCGGCTCCGC
CACATCAAGCGCTCCGCCAGGGATCTGCGAGGAAGCCGCTACTCCAACCCAGCCTACCTCTGGTG
CTCCGTCCTAGCAAAGCCCTGCACAGACTCCAGCCGAGCCACACCTGGCTATGAGGTGGCCAGCG
AAGCGCCTCATCTCTCGGTGGAGGACTTCACCGAGTTGTGTGA

(Double underline indicates bases bordering the splice junction)

33

TABLE 15

Primer across the junction between
TSC2 exon 18 and 20

Table 23. Primer sequences CTTGAAAGCAGCTTCAGGCC
across the junction between
TSC2 exon 18 and 20
(SEQ ID No. 33)

(Double underline indicates bases bordering the splice junction)

TABLE 16

siRNA for selectively knockdown TSC2 full
length and variant expression

siRNA targeting TSC2 exon 19

Sense (SEQ ID No. 31) 5' CUGCGCUUAAAAGUGGUCAdTdT
3'

34

TABLE 16-continued

siRNA for selectively knockdown TSC2 full
length and variant expression

5

Antisense (SEQ ID No. 32) 3' dTdTGACCGGAUUUUCACG-
AGU (5'-P) 5'

10

siRNA targeting the junction between
TSC2 exon 18 and exon 20

15

Sense (SEQ ID No. 35) 5' GAAGCAGUUUCAGGCCdTdT
3'

15

Antisense (SEQ ID No. 36) 3' dTdTCUUCGUCGAAAGUCCG-
GGU (5'-P) 5'

(Double underline indicates bases bordering the splice junction)

TABLE 17

RASGRP2 (full length) Nucleotide Sequence (1830 nt, SEQ ID No. 37)

ATGGCAGGCCACCCTGGACACTGGACAAGGGCTGCACGGTGGAGGAGCTGCTCCGCGGGTGCATCGAACGCTTC
GATGACTCCGGAAGGTGCGGGACCCGCAGCTGGTGCATGTTCTCATGATGCACCCCTGGTACATCCCC
TCCCTCAGCTGGCGCCAAGCTGCTCCACATCTACCAACAATCCGGAAGGACAACCTCAAATTCCCTGCAG
GTGAAAACGTGCCACCTGGTCAAGGACTGGATCTCCGCTCCAGCGGAGTTGACTTGAACCCGGAGTTG
GCTGAGCAGATCAAGGAGCTGAAGGCTCTGCTAGACCAAGAAGGAAACCGACGGCACAGCAGCTTAATCGAC
ATAGACAGCGTCCCTACCTACAAGTGGAAAGCGCAGGTGACTCAGCGAACCCGTGGGACAGAAAAGCGC
AAGATGTCCCTGTTGTTGACCACCTGGAGCCATGGAGCTGGCGGAGCATCTCACCTACTTGGAGTATCGC
TCCCTCTGCAAGATCCTGTTGAGACTATCACAGTTCTGACTCATGGCTGACTGTGGACAACCCCGTC
CTGGAGCGGTTCATCTCCCTTCAACAGCGTCTCACAGTGGTGCAGCTCATGATCCTCAGCAAACCCACA
GCCCGCAGCGGGCCCTGGTCACTCACACACTTGTCCACGTGGCGAGAACGCTGCTACAGCTGCAGAACTTC
AACACGCTGATGGCAGTGGCTGGGGCCTGAGGCCACAGCTTCACTCCGCTCAAGGAGACCCACAGCCAC
GTTAGCCCTGAGACCATCAAGCTCTGGAGGGCTCACGGAACTAGTGACGGCGACAGGCAACTATGGCAAC
TACCGCGTGGCTGGCAGCCCTGTGTGGGCTTCCGATCCTGGGTGTGCACCTCAAGGACCTGGT
GCCCTGCAGCGGACTGCGCTGACTGGCTGGACCCAGCGGGACCCGGCTAACGGGCAAGATGAAGCAG
CTCTTTAGCATCCTGGAGGAGCTGGCATGGTGCACCGCTGCGGCCACCGAGTACAGGCCAACCCGACCTG
CTGAGCCTGCTCACGGTGTCTGGATCAGTACAGACGGAGGATGAGCTGTACCGCTGTCCCTGCAGCG
GAGCCGCGCTCCAAGTCCCTGCCAACCGCCCCACAGAGTTGCACCCACCAACCCGGCCCCGGTACTGGAG
GAGTGGACCTCGGCTGCCAACCAAGCTGGATCAGGCCCTCGTGGTGGAGCAGATCGAGAAGATGGTGGAG
TCTGTGTTCCGGAACCTTGACGTCGATGGGATGGCCACATCTCACAGGAAGAATTCCAGATCATCCGTGG
AACTTCCCTTACCTCAGCGCTTGGGACCTCGACCAACAGGAGATGGCTGCATCAGCAGGGAGGAGATG
GTTTCCTATTCCTGCGCTCCAGCTCTGTGTTGGGGGGCGATGGCTCGTACACAACCTCCAGGAGAGC
AACTCCTGCGCCCCGTCGCGCTGCCACTGCAAAGCCCTGATCCTGGGATCTACAAGCAGGGCTCAA
TGCGAGCCTGTGGAGTGAACCTGCCACAAGCAGTGCAAGGATCGCCTGTCAGTTGAGTGTGGCGCAGGGCC

TABLE 17-continued

RASGRP2 (full length) Nucleotide Sequence (1830 nt, SEQ ID No. 37)	
CAGAGTGTGAGCCTGGAGGGCTGCACCCCTCACCATGCACAGCACCACATCACCGCGCCTTCAGC	
TTCTCTGCCCGCCCTGGCAGGCGAGGCTCCAGGCCTCCAGAGATCCGTGAGGAGGAGGTACAGACGGTG	
GAGGATGGGTGTTGACATCCACTTGTAA	

(Exon 10 is indicated by double underline. Exon 11 is indicated by wave underline.)

TABLE 18

RASGRP2 variant 1 (lacking exon 10) Nucleotide Sequence (1707 nt, SEQ ID No. 45)	
ATGGCAGGCACCCCTGGACCTGGACAAGGGCTGCACGGTGGAGGAGCTGCT	15
CCGCGGGTGCATCGAACGCTTCGATGACTCCGGAAAGGTGCGGGACCCGC	
AGCTGGTGCATGTTCTCATGATGCACCCCTGGTACATCCCTCTCT	20
CAGCTGGCGCCAAGCTGCTCCACATCTACCAACAATCCCGGAAGGACAA	
CTCCAATTCCCTGCAGGTGAAAACGTGCCACCTGGTCAGGTACTGGATCT	
CCGCCTTCCCAGCGGAGTTGACTTAACCCGGAGTTGGCTGAGCAGATC	
AAGGAGCTGAAGGCTCTGCTAGACCAAGAAGGGAACCGACGGCACAGCAG	
CCTAATCGACATAGACAGCGTCCCTACCTACAAGTGGAAAGCGCGAGGTGA	
CTCAGCGGAACCCCTGTGGGACAGAAAAAGCGCAAGATGTCCCTGTTGTT	30
GACCACCTGGAGGCCATGGAGCTGGCGGAGCATCTCACCTACTTGGAGTA	
TCGCTCCTCTGCAAGATCCTGTTCAAGGACTATCACAGTTCGTGA	
ATGGCTGCACTGTGGACAACCCCGTCTGGAGCGGTTCATCTCCCTCTC	
AAACAGCGTCTCACAGTGGTGAGCTCATGATCCTCAGCAAACCCACAGC	35
CCCGCAGGGCCCTGGTCATCACACACATTGTCACGTGGCGGAGAAC	
TGCTACAGCTGAGAACATTCAACACGCTGATGGCAGTGGTGGGGCCTG	
AGCCACAGCTCCATCTCCGCTCAAGGAGACCCACGCCACGTTAGCCC	40
TGAGACCATCAAGCTCTGGAGGGTCTACGGAACTAGTGACGGCGACAG	
GCAACTATGGCAACTACCGGCGTGGCTGGCAGCCTGTGTGGGCTCCGC	
TTCCCGATCCTGGGTGTCACCTCAAGGACCTGGTGGCCCTGCAGCTGG	45
ACTGCTGACTGGCTGGACCCAGCCCGACCCGCTCAACGGGGCAAGA	
TGAAGCAGCTTTAGCATCCTGGAGGAGCTGCCATGGTACCGCTG	
CGGCCACCAAGTACAGGCCAACCCGACCTGCTGAGCCTGCTACGGTGT	
TCTGGATCAGTATCAGACGGAGGATGAGCTGACCGCTGTCAGCTGCAGC	50
GGGAGCGCGCTC <u>AAAGTCCTCGTGTGTTCCG</u> AACTTGACGTCGAT	
GGGGATGCCACATCTCACAGGAAGAATTCCAGATCATCCGTGGGAACTT	
CCCTTACCTCAGCGCCTTGGGACCTCGACCGAGAACCCAGGATGGCTGA	
TCAGCAGGGAGGAGATGGTTCTATTCCTGCGCTCCAGCTGTGTTG	55
GGGGGGCGATGGCTTCGTACACAACCTCCAGGAGAGCAACTCCTTGC	
CCCCGTGCCCTGCCACTGCAAAGCCCTGATCCTGGGATCTACAAGC	
AGGGCCTCAAATGCCGAGCCTGTGGAGTGAAC TGCCACAAGCAGTGAAG	
GATCGCCTGTCAGTTGAGTGTGGCGCAGGGCCCAGAGTGTGAGCCTGG	60

TABLE 18-continued

RASGRP2 variant 1 (lacking exon 10) Nucleotide Sequence (1707 nt, SEQ ID No. 45)	
GGGGCTGCACCCCTCACCCATGCACAGCACCACATCACCGCGCT	15
TCAGCTCTCTCTGCCCGCCCTGGCAGGCGAGGCTCCAGGCCTCCAGAG	
ATCCGTGAGGAGGAGGTACAGACGGTGGAGGATGGGTGTTGACATCCA	
CTTGTA	
(Double underline indicates bases bordering the splice junction)	
25	

TABLE 19

RASGRP2 variant 2 (lacking exon 11) Nucleotide Sequence (1714 nt, SEQ ID No. 49)	
ATGGCAGGCACCCCTGGACCTGGACAAGGGCTGCACGGTGGAGGAGCTGCT	30
CCGCGGGTGCATCGAACCTTCGATGACTCCGGAAAGGTGCGGGACCCGC	
AGCTGGTGCATGTTCTCATGATGCACCCCTGGTACATCCCTCTCT	
CAGCTGGCGCCAAGCTGCTCCACATCTACCAACAATCCCGAAGGACAA	35
CTCCAATTCCCTGCAGGTGAAAACGTGCCACCTGGTCAGGACTAGGGATCT	
CCGCCTTCCCAGCGGAGTTGACTTAACCCGGAGTTGGCTGAGCAGATC	
AAGGAGCTGAAGGCTCTGCTAGACCAAGAAGGGAACCGACGGCACAGCAG	40
CCTAATCGACATAGACAGCGTCCCTACCTACAAGTGGAAAGCGGCAGGTGA	
CTCAGCGGAACCCCTGTGGGACAGAAAAAGCGCAAGATGTCCCTGTTGTT	
GACCACCTGGAGGCCATGGAGCTGGCGGAGCATCTCACCTACTTGGAGTA	45
TCGCTCCTCTGCAAGATCCTGTTCAAGGACTATCACAGTTCGTGA	
ATGGCTGCACTGTGGACAACCCGTCCTGGAGCGGTTCATCTCCCTCTC	
AAACAGCGTCTCACAGTGGTGAGCTCATGATCCTCAGCAAACCCACAGC	50
CCCGCAGGGCCCTGGTCATCACACACTTGTCCACGTGGCGAGAAC	
TGCTACAGCTGAGAACCTCAACACGCTGATGGCAGTGGTGGGGCTCG	
AGCCACAGCTCCATCTCCGCTCAAGGAGACCCACGCCACGTTAGCCC	55
TGAGACCATCAAGCTCTGGAGGGTCTACGGAACTAGTGACGGCGACAG	
GCAACTATGGCAACTACCGGCGTGGCTGGCAGCCTGTGTGGCTCCGC	
TTCCCGATCCTGGGTGTCACCTCAAGGACCTGGTGGCCCTGCAGCTGG	60
ACTGCCTGACTGGCTGGACCCAGCCCGACCCGCTCAACGGGGCAAGA	
TGAAGCAGCTTTAGCATCCTGGAGGAGCTGCCATGGTACCGCTG	
CGGCCACCAAGTACAGGCCAACCCGACCTGCTGAGCCTGCTCACGGTGC	
TCTGGATCAGTATCAGACGGAGGATGAGCTGACCGCTGAGCTGTACCC	65

TABLE 19-continued

RASGRP2 variant 2 (lacking exon 11)
Nucleotide Sequence (1714 nt, SEQ ID No. 49)
GGGAGCCCGCCTCAAGTCCTCGCCAACCAGCCCCACGAGTTGCACCCCA
CCACCCCGCCCCGGTACTGGAGGAGTGGACCTCGCTGCCAACCAA
GCTGGATCAGGGCCCTCGTGGTGGAGCACATCGAGA <u>AAGATGGTGGAGGGAT</u>
<u>GGCTGCATCAGCAGGGAGGAGATGGTTCTATTTCCTGCGCTCCAGCTC</u>
TGTGTTGGGGGGCGCATGGCTTCTGACACA <u>ACTTCCAGGAGAGCAACT</u>
CCTTGCGCCCCGCGCTGCCACTGCAA <u>AGCCCTGATCCTGGGCATC</u>
TACAAGCAGGGCTCAA <u>ATGCGAGCCTGTGGAGTGA</u> ACTGCCAACAGCA
GTGCAAGGATCCCTGTCAGTTGAGTGTGCGCGCAGGGCCCAGAGTGTGA
GCCTGGAGGGTCTGCACCCTCACCCATGCACAGCCACCATCAC
CGCGCCTCAGCTCTCTCTGCCCGCCCTGGCAGGGCAGGGCTCCAGGCC
TCCAGAGATCCGTGAGGAGGAGGTACAGACGGTGGAGGATGGGGTGTGTTG
ACATCCACTTGTAA

(Double underline indicates bases bordering the splice junction)

TABLE 20

Primer across the junction between RASGRP2 variants
Primer across junction <u>CAAGTCCTCGTCTGTGTTCC</u>
between RASGRP2 exon 9 and exon 11 (SEQ ID No. 44)
Primer across junction <u>GATGGTGGAGGGATGGCTGC</u>
between RASGRP2 exon 10 and exon 12 (SEQ ID No. 48)

(Double underline indicates bases bordering the splice junction)

TABLE 21

sirNA for selectively knockdown RASGRP2 full length and variants expression
sirNA targeting RASGRP2 exon 10
Sense (SEQ ID No. 40) : 5' GUGGAGCACAU <u>CGAGAGAAdTdT</u> 3'
Antisense (SEQ ID No. 41) : 3' dTdT <u>ACCUUCGUGUAGCUC-</u> UUUC (5'-P) 5'
sirNA targeting RASGRP2 exon 11
Sense (SEQ ID No. 42) : 5' CCACAU <u>UCACAGGAAGAAdTdT</u> 3'
Antisense (SEQ ID No. 43) : 3' dTdT <u>GGGUAGAGUGUUCU-</u> UCUU (5'-P) 5'
sirNA targeting junction between RASGRP2 exon 9 and 11:
Sense (SEQ ID No. 46) : 5' CCUC <u>CGUUCUGUUCGGAAAdTdT</u> 3'

TABLE 21-continued

5	sirRNA for selectively knockdown RASGRP2 full length and variants expression
5	Antisense (SEQ ID No. 47) : 3' dTdT <u>GGAGCAGCACACAGG-</u> CCUU (5'-P) 5'
10	sirRNA targeting junction between RASGRP2 exon 10 and 12
10	Sense (SEQ ID No. 50) : 5' GGUGG <u>AGGAUGGCUGCAudTdT</u> 3'
15	Antisense (SEQ ID No. 51) : 3' dTdT <u>CCACCUCCUACCGA-</u> CGUA (5'-P) 5'
15	(Double underline indicates bases bordering the splice junction)
20	ITGA4 (full length) Nucleotide Sequence (3099 nt, SEQ ID No. 52)
20	ATGGCTGGAGCGAGGCGCGAACCCGGCCCCGAAGGGCCGCCGTCCG
25	GGAGACGGTGTGCTGTGCTGCCCTGGGGTCCCGACGGCCGCCCT
25	ACAA <u>CGTGGACACTGAGAGCGCCTGCTTACCA</u> GGCCCCAACACAG
30	CTGTCGGCTACTCGGTGTGCGACAGCCACGGGCGAACCGATGGCT
30	CCTAGGGTGC <u>GGCCACTGCCA</u> CTGGCTGCCAACGCTTCAGTGATCA
35	ATCCC <u>GGGGCGATTACAGATCGAGGATCGGAAAGAATCCGGCCAGACG</u>
35	TGCGAACAGCTCAGCTGGTAGCCCTAA <u>GGAGAACCTGTGGAAGAC</u>
35	TTGTTGGAGAGAGACAATCAGTGGTGGGGTACACTTCCAGAC
35	AGCCAGGAGAAA <u>ATGGATCCATCGTGA</u> CTGTGGCATA <u>GGAAAGAAT</u>
40	ATATTTACATAAGA <u>ATGAAATAAGCTCCC</u> ACTGGTGGTGATGG
40	AGTGCCCCCTGATTACGAACAGAA <u>CTGAGTAAAGAATAGCTCCGTGTT</u>
40	ATCAAGATTATGTGAAAAA <u>TTGGAGAAA</u> TTTGATCATGTCAAGCT
40	GGAATATCCAGTTTACACAA <u>AGGATTA</u> ATTGTGATGGGGCCCCAGG
45	ATCATCTTACTGGACTGGCTCTCTTTGTCTACAATATAACTACAAATA
45	AATA <u>CAAGGCTTTAGACAAACAA</u> ATCAAGTAA <u>TTGGAA</u> TT
45	TTAGGATATT <u>CGTCGAGCTGG</u> CTTCGAGCAGACTACCGA
50	AGTAGTCGGAGGAGCTCTCAACATGAGCAGATTGGTAAGGCATA <u>ATAT</u>
50	TCAGCATTGATGAAA <u>AGAAACTAA</u> ATCTTACATGAA <u>ATGAAAGGTAA</u>
50	AAGCTTGGATCGTACT <u>TTGGAGCTCTGTCTGTGCTGTGGACCTCA</u> ATGC
55	AGATGGCTCTCAGAT <u>CGTGGAGCACCC</u> ATGCAGAGCACCATCA
55	GAGAGGAAGGAAGAGTGGTGTACAT <u>CAACTCTGCTCGGAGCAGTA</u>
55	ATGAAT <u>CGAATGGAAACAAAC</u> CTCGTGGAGCACA <u>AAATATGCTGCAAG</u>
60	ATTTGGGAAT <u>CTATGTTA</u> ATTCTGGCGACATTGACA <u>ATGATGGCTTG</u>
60	AAGATGGTGT <u>CGGAGCTCCACAA</u> AGAGATGACT <u>TGCAAGGTGCTATT</u>
60	TATATT <u>TACAATGGCCGTG</u> CAGATGG <u>ATCTGTC</u> AC <u>CTTCTCACAGAG</u>
65	AATTGAAGGACTTCAG <u>ATCGCAAATGTTA</u> AGTATG <u>GGACAGTCTA</u>
65	TATCAGGACAA <u>ATTGATGCGAGATA</u> AA <u>GGCTATG</u> AGATG <u>TAGCAGTT</u>
65	GGTGC <u>TTTCGGTCTGATTCTGCTGTGCTTGCTAAGGACAAGAC</u> CTGTAGT

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TABLE 22-continued

ITGA4 (full length) Nucleotide Sequence (3099 nt, SEQ ID No. 52)	
AATTGTTGACGCTTCTTAAGCCACCCCTGAGTCAGTAAATAGAACGAAAT	
TTGACTGTGTTGAAAATGGATGCCCTCTGTGTCATAGATCTAACACTT	
TGTTTCTCATATAAGGGCAAGGAAGTTCAGGTTACATTGTTGTTTA	
TAACATGAGTTGGATGTAAACAGAAAGGCAGAGTCTCCACCAAGATTCT	
ATTTCCTCTAATGAACTCTGACGTGATTACAGGAAGCATAACAGGTG	
TCCAGCAGAGAAGCTAACTGTAGAACACATCAAGCATTATGCGGAAAGA	
TGTGCGGGACATCCTCACCCCAATTCAAGATTGAGCTGCTTACCACTTG	
GTCCTCATGTCACTGAAACAGAACAGAGAATTCCCACCACTTCAG	
CCAATTCTCAGCAGAAGAAAGAAAAAGACATAATGAAAAAACATAAAA	
CTTGCAGGGTTTGCCCCATGAAAATTGTTCTGCTGATTACAGGTTT	
CTGCAAAGATTGGTTTGAGGCCCCATGAAAATAAAACATATCTTGTG	
<u>GTGGGAGTATGAA</u> AGACATTGATGTTGAATGTCCTGTTAATGCTGG	
<u>AGATGATGCA</u> TATGAAACGACTCATGTCAAACATCCGGGCTTT	
<u>ATTCATTAAG</u> ATTTAGAGCTGAAAGAGAACGAAATAACTGTGAAGTC	
ACAGATAACTCTGGCGTGGTACAACATTGACTGCACTATTGGCTATATATA	
TGTAGATCATCTCAAGGATAGATATTAGCTTCTCTGGATGTGAGCT	
CACTCAGCAG <u>CGGAAGGGACCTCAGTATC</u> ACAGTCATGCTACCTGT	
GAAAATGAAGAGGAAATGGACAATCTAAAGCACAGCAGAGTGAATGTAGC	
ATAACCTTAAATATGAGGTTAACGCTGACTGTTCATGGTTGTAAACC	
CAACTCATTGTATGGATCAAATGATGAAAATGAGCTGAAACGTGC	
ATGGTGGAGAAAATGAACCTAACCTTCATGTTATCAACACTGGCAATAG	
TATGGCTCCCAATGTTAGTGTGAAATAATGGTACCAAATTCTTTAGCC	
CCCAAACGTATAAGCTGTTAACATTGGATGTCCAGACTACTGG	
GAATGCCACTTGAAAATTATCAAAGAGTGTGTCATTAGAGCAGCAAA	
GAGTGCATGAGACCTGAAAGGCATAGTCCGGTTCTGTCCAAGACTG	
ATAAGAGGCTATTGACTGCATAAAAGCTGATCCACATTGTTAAATTCT	
TTGTGTAATTGGAAAATGGAAAGTGGAAAAGAACGCCAGTGTTCATAT	
CCAACTGGAGGCCATCCATTAGAAATGGATGAGACTTCAGCAC	
TCAAGTTGAAAATAGAGCAACAGGTTTCCAGAGCCAATCCAAGAGTA	
ATTGAACTAAACAAGGATGAGAATGTTGCGCATGTTCACTGGAAGGACT	
ACATCATCAAAGACCCAAACGTTATTCACCATAGTGAATTTCAGTA	
GCTTGCTACTGGACTTATTGACTCTATTGATCTCATATGTTATGTGG	
AAGGCTGGCTTCTTAAAAGACAATACAAATCTATCCTACAAGAAGAAAA	
CAGAAGAGACAGTGGAGTTATCAACAGTAAAGCAATGATGATTAA	

(Exon 23 is indicated by double underline.)

40

TABLE 23

ITGA4 variant (lacking exon 23) Nucleotide Sequence (2948 nt, SEQ ID No. 58)	
5 ATGGCTTGGGAAGCGAGGCGCGAACCCGCCCGAAGGGCGCCGTCG	
GGAGACGGTGTGCTGCTGCGCTGGGGTCCGACCGGCCGCCCT	
ACAAACGTGGACACTGAGAGCGCTGCTTACAGGCCCCACAACACG	
10 CTGTTCGGCTACTCGGTGCTGTCAGGCCACGGGCGAACCGATGGCT	
CCTAGGGTGCCTCACTGCCAACGCTCGCAACGCTTCAGTGTATCA	
ATCCCGGGCGATTACAGATCGAGGATCGGAAAGAATCCGGCCAGACG	
15 TGCGAACAGCTCCAGCTGGTAGCCCTAATGGAGAACCTTGTGAAAGAC	
TTGTTGGAAGAGAGAGACAATCAGTGGTTGGGGTACACTTCCAGAC	
AGCCAGGAGAAAATGGATCCATCGTGTGAGATGGAAAGAAT	
20 ATATTTACATAAAAGAATGAAAATAAGCTCCCACTGGTGGTTGTATGG	
AGTGCCTCCGTATACGAACAGAACTGAGAAAAGAATAGCTCCGTGTT	
ATCAAGATTATGTGAAAAATTGGAGAAAATTGATCATGTCAAGCT	
25 GGAATATCCAGTTTACACAAAGGATTAATTGTGATGGGGCCAGG	
ATCATCTTACTGGACTGGCTCTCTTGTCTACAATATAACTACAAATA	
AATAACAAGGTTTTAGACAAACAAATCAAGTAAATTGGAGATTAT	
TTAGGATATTCACTCGAGCTGGTCACTTCGGAGCCAGCATACTACCGA	
30 AGTAGTCGGAGGAGCTCTCAACATGAGCAGATTGTAAGGCATATAT	
TCAGCATTGATGAAAAAGAACTAAATATCTACATGAAATGAAAGTAA	
AAGCTTGGATCGTACTTGGAGCTCTGTGCTGCTGGACCTCAATGC	
35 AGATGGCTCTCAGATCGCTGGAGCACCCATGAGCAGCACCACATCA	
GAGAGGAAGGAAGAGTGTGTTGTACATCAACTCTGGCTGGAGCAGTA	
ATGAATGCAATGAAAACAAACCTCGTGGAGTGAACAAATATGCTGCAAG	
40 ATTGGGAAATCTAGTTAATCTGGCAGATTGACAATGATGGCTTG	
AAGATGTTGCTATCGGAGCTCCACAAGAAGATGACTTGCAAGGTGCTATT	
TATATTACAATGGCCGTGAGATGGATCTGTCACCTTCACAGAG	
45 AATTGAAGGACTTCAGATCAGCAAATCGTTAGTATGTTGGACAGCTA	
TATCAGGACAAATGATGCAAGATAATAATGGCTATGAGATGAGCAGTT	
GGTGTCTTCGGCTGATTCTGCTGCTGTAAGGACAAGACCTGTAGT	
50 AATTGTTGACGCTTCTTAAGCCACCTGAGTCAGTAAATAGAACGAAAT	
TTGACTGTGTTGAAAATGGATGGCTCTGTGTCAGATCTAACACTT	
TGTTTCTCATATAAGGGCAAGGAAGTCCAGGTTACATTGTTGTTTA	
55 TAACATGAGTTGGATGTGAACAGAAAGGCAGAGTCTCCACCAAGATTCT	
ATTCTCTTCTAATGAAACTCTGACGTGATTACAGGAAGCATAACAGGTG	
TCCAGCAGAGAAGCTAACTGTAGAACACATCAAGCATTATGCGGAAAGA	
TGTGCGGGACATCCTCACCCCAATTCAAGTGAAGCTGCTTACCACTTG	
60 GTCTCATGTCACTGAAACGAGTACAGAGGAATTCCACCACTTCAG	
CCAATTCTCAGCAGAAGAAAAGACATAATGAAAAAACAAATAAA	
CTTGCAAGGTTTGCCATGAAAATTGTTCTGCTGATTACAGGTT	
65 CTGCAAAGATTGGGTTTGAGAAGAGAAGCAAAACTGTGAAGTC	

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TABLE 23-continued

ITGA4 variant (lacking exon 23) Nucleotide Sequence (2948 nt, SEQ ID No. 58)	
CAGATAACTCTGGCGTGGTACAACCTGACTGCAGTATTGGCTATATAT	
GTAGATCATCTCTCAAGGATAGATATTAGCTTCTCCTGGATGTGAGCTC	
ACTCAGCAGAGCGGAAGAGGACCTCAGTATCACAGTCATGCTACCTGTG	
AAAATGAAGAGGAAATGGACAATCTAAAGCACAGCAGAGTGAATGTAGCA	
ATACCTTTAAATATGAGGTTAACGACTGACTGTTCATGGGTTGTAACCC	
AACTTCATTTGTGTATGGATCAAATGATGAAAATGAGCCTGAAACGTGCA	
TGGTGGAGAAAATGAACTTAACTTCCATGTTATCAACACTGGCAATAGT	
ATGGCTCCCAATGTTAGTGTGAAATAATGGTACCAAATTCTTTAGCCC	
CCAAACTGATAAGCTGTTCAACATTTGGATGTCCAGACTACTACTGGAG	
AATGCCACTTGAAAATTATCAAAGAGTGTGTCATTAGAGCAGCAAAAG	
AGTGCAATGCAGACCTGAAAGGCATAGTCCGGTTCTGTCCAAGACTGA	
TAAGAGGCTATTGACTGCATAAAAGCTGATCCACATTGTTAAATTCT	
TGTGTAATTTGGAAAATGGAAAGTGGAAAAGAAGCCAGTGTTCATATC	
CAACTGGAAAGGCCGCCATCCATTAGAAATGGATGAGACTTCAGCACT	
CAAGTTGAAATAAGAGCAACAGGTTTCCAGAGCCAATCCAAGAGTAA	
TTGAACTAAACAAGGATGAGAATGTTGCGCATGTTCACTGGAAAGGACTA	
CATCATCAAAGACCCAAACGTTATTCACCATAGTGAATTTCAGTAG	
CTTGCTACTTGGACTTATTGACTTCTATTGATCTCATATGTTATGTGGA	

42

TABLE 23-continued

ITGA4 variant (lacking exon 23) Nucleotide Sequence (2948 nt, SEQ ID No. 58)	
5 AGGCTGGCTTCTTAAAGACAATACAAATCTATCCTACAAGAAGAAAAC	
AGAAGAGACAGTGGAGTTATCAACAGTAAAAGCAATGATGATTAA	

(Double underline indicates bases bordering the splice junction)

10

TABLE 24

Primer across the junction between ITGA4 exon 22 and 24	
15 15 Primer across the junction <u>GGGTTTTGAAAGAAGAAGC</u> between ITGA4 exon 22 and 24 (SEQ ID No. 57)	

(Double underline indicates bases bordering the splice junction)

20

TABLE 25

siRNA for selectively knockdown ITGA4 full length and variants expression	
25 25 siRNA targeting ITGA4 exon 23	

Sense (SEQ ID No. 55) 5' GGGAGUAUGAAGACAUUGA dTdT 3'

30 Antisense (SEQ ID No. 56) 3' dTdTCCCCUCAUACUUUCUGUA- ACU (5'-P) 5'

siRNA targeting splice junction between ITGA4 exon 22 and exon 24

35 Sense (SEQ ID No. 59) 5' GAAGAAGAGAAGCAAAUAA dTdT 3'Antisense (SEQ ID No. 60) 3' dTdTCUUUCUCUUUCGUUU- AUU (5'-P) 5'

(Double underline indicates bases bordering the splice junction)

TABLE 26

MET (Full length) Nucleotide Sequence (4226 nt, SEQ ID No. 62)
ATGAAGGCCCCGCTGTGCTTCACCTGGCATCCTCGTCTCTGTTACCTGGTGCAGAGGAGCAATGGG
AGTGTAAAGAGGCACTAGCAAAGTCCGAGATGAATGTGAATATGAAGTATCAGCTCCCAACTTCACCGCGG
AAACACCCATCCAGAATGTCATTCTACATGAGCATCACATTTCCTGGTGCCTAACTACATTTATGTT
TAAATGAGGAAGACCTTCAGAAGGTTGCTGAGTACAAGACTGGGCCTGTGCTGGAAACACCCAGATTGTTCC
CATGTCAGGACTGAGCAGCAAAAGCCAATTATCAGGAGGTGTTGGAAAGATAAACATCAACATGGCTCAG
TTGTCGACACCTACTATGATGATCAACTCATAGTGTGGCAGCGTCAACAGAGGGACCTGCCAGCGACATG
TCTTCCCCACAATCATACTGCTGACATACAGTCGGAGGTTCACTGCATATTCTCCCCACAGATAGAAGAGC
CCAGGCCAGTGCCTGACTGTGTTGAGCAGCCCTGGGAGCCAAAGTCCTTCATCTGTAAAGGACCGGTTCA
TCAACTTCTTGTAGGCAATACCATAAATTCTTCTATTCCAGATCATCCATTGCTCATCTGAGATTCAGTGA
GAAGGCTAAAGGAAACGAAAGATGGTTTATGTTTGACGGACCAGTCTACATTGATGTTTACCTGAGT
TCAGAGATTCTTACCCATTAAGTATGTCATGCCTTGGAAAGCAACAATTATTTACTCTCTGACGGTCC
AAAGGGAAACTCTAGATGCTCAGACTTTCACACAAGAATAATCAGGTTCTGTTCCATAAACTCTGGATTG
ATTCCCTACATGGAAATGCCTCTGGAGTGTATTCTCACAGAAAAGAGAAAAAGAGATCCACAAAGAAGGAAG

TABLE 26-continued

MET (Full length) Nucleotide Sequence (4226 nt, SEQ ID NO. 62)
TGTTTAATATACTTCAGGCTGCATGTCAGCAAGCCTGGGCCAGCTTGCTAGACAAATAGGAGCCAGCC TGAATGATGACATTCTTCGGGTGTCGACAAAGCAAGCCAGATTCTGCCAACCAATGGATCGATCTG CCATGTGTGCATTCCTATCAAATATGTCACAGACTCTTCACAAGATGTCAACAAAAAATGTGAGAT GTCTCCAGCATTTCAGGACCCAATCATGAGCACTGCTTAAAGGACACTTCTGAGAAATTCACTCAGGCT GTGAAGCGCCGCTGATGAATATCGAACAGAGTTACCACAGCTTGCAGCGCTGACTTATTCACTGGTC AATTCAAGCGAAAGTCCTTTAACATCTATCCACCTTCATTAAGGAGACCTCACCATAGCTAATCTGGGA CATCAGAGGGTCGCTTCATGCAGGTTGTCGATCAGGACCATCAACCCCTCATGTGAATTTCCTCC TGGACTCCCACCCAGTGTCTCCAGAAGTGATTGAGCATACTAAACAAAATGGCTACACACTGGTTA TCACTGGGAAGAAGATCACGAAGATCCCATTGAATGGCTGGGCTGCAGACATTCCAGTCAGTCAAT GCCCTCTGCCCCACCCCTTGTTCAGTGTGGCTGGCACGACAAATGTGCGATCGAGGAATGCCTGA GCGGGACATGGACTCAACAGATCTGCTGCCTGCAATCTACAAGGTTCCAAAATAGTCACCCCTTGAAG GAGGGACAAGGCTGACCATATGGCTGGACTTGGATTTCGGAGGAATAATAAATTGATTAAAGAAAA CTAGAGTCTCTGGAAATGAGAGCTGCACCTTGACTTAAGTGAGAGCACGATGAATACATTGAAATGCA CAAGTTGGTCTGCCATGAATAAGCATTCAATATGCCATAATTATTCAAATGCCACGGACAACACAAT ACAGTACATTCTCTATGTGGATCCTGTAATAACAAGTATTCGCCAACATGGCTATGGCTGGC CTTTACTTAACTGGAAATTACCTAACAGTGGAAATTCTAGACACATTCAATTGGTGGAAAACAT GTACTTTAAAAGTGTCAACAGTATTCTGAAATGTTACCCAGCCAAAACCATTCAACTGAGTTG CTGTTAAATTGAAAATTGACTTAGCCAACCGAGAGACAAGCATTCACTGAGTACCCATTGTCT ATGAAATTCACTAACCAACCAATTCTTTATTAGTACTGGTGGAAAAGAACCTCTCAACATTGCA TTTGCTTGCCAGTGGTGGAGCACAATAACAGGTGTTGGAAAAACCTGAATTCACTGAGTTGGCT TGGTCATAAAATGTCATGAAGCAGGAGGAACCTTACAGTGGCATGTCACATCGCTTAATTCA TCTGTTGTACCACTCCTCCCTGCAACAGCTGAATCTGCAACTCCCCCTGAAAACCAAGC TAGATGGGATCCTTCAAATCTTGATCTCATTATGTACATAATCCTGTTAAGCCTTTGAAAGC CAGTGATGATCTCAATGGCAATGAAAATGTACT <u>GGAAATTAGGGAAATGAATTGACCTGAAGCAGTTA</u> AAGGTGAAGTGTAAAAGTGGAAATAAGAGCTGTGAGAAATAACACTTACATTCTGAAGCC CGGTCCCCAATGACCTGCTGAAATTGAACAGCGAGCTAAATAGAGTGGAAAGCAAGCA TCCTGGAAAAGTAATAGTTCAACCAGATCAGAATTTCACAGGATTGATTGCTGGTGTCTCA CAGCACTGTTATTACTACTGGTTTCTGTGGTGGAAAAGAGAAAGCAATTAAAGATCTGG AATTAGTCGCTACGATGCAAGAGTACACACTCCTCATTGGATAGGCTTGTAAAGT CAACTACAGAAATGGTTCAAATGAATCTGAGACTACCGAGCTATTCCAGAAGATCAG CATCTCAGAACGGTTCATGCCAACAGTGCAGTATCCTCTGACAGACATG ACTCTGATATATCCAGTCATTACTGCAAAATACTGTCACATTGACCTCAGTG TCCAGGCACTGAGCATGTAGTGGTGGCCAGTAGCCTGATTGCTG GGCATTGGTGTATATCATGGACTTGGACAATGATGGCAAGAAAATC CCTTGAAACAGAACTGACATAGGAGAAGTTCCAATTCTGACCGAG GTCATCCCAATGCCCTCGCTGGAAATCGCCTGCGAACAGTGG ACATGAAACATGGAGATCTCGAAATTCACTGAAATGAGACT GCTTGGTCTCAAGTAGCCAAGGATGAAATCTTGCAAG CAAGAAAATGTATGCTGGATGAAAATTCA CAAGTCAAGGTTGCTGATTGGCTTG CAAGAGACATGTATG

TABLE 26-continued

MET (Full length) Nucleotide Sequence (4226 nt, SEQ ID No. 62)

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ATAAAGAAATACTATAGTGTACACAACAAAACAGGTGCAAAGCTGCCAGTGAAAGTGGATGGCTTGAAAGTC
TGCAAACTCAAAGTTACCACCAAGTCAGATGTGTGGCCTTGGCGTGCTCCTCTGGGAGCTGATGACAA
GAGGAGCCCCACCTTATCCTGACGTAACACCTTGTATATACTGTTACTTGTGCAAGGGAGAACACTCC
TACAACCCGAATACTGCCAGACCCCTTATGAAGTAATGCTAAATGCTGGCACCCCTAAAGCCGAAATGC
GCCCATCCTTCTGAACTGGGTCCGGATATCAGCGATCTCTACTTCAATTGGGAGCACTATGTCC
ATGTGAACGCTACTTATGTGAACGTAACATGTGCTCCGTATCCTCTGTGTCATCAGAAAGATAACG
CTGATGATGAGGTGGACACACGACCAGCCTCTGGGAGACATCATAG

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(Double underline indicates bases bordering the splice junction between exon 26 and 28)

TABLE 27

MET variant (with non-coding exon 27) Nucleotide Sequence (4651 nt, SEQ ID No. 65)

```

ATGAAGGCCCCGCTGTGCTTGCACCTGGCACCTCGTGCCTGTTACCTGGTGAGAGGAGCAATGGG
AGTGTAAAGAGGCCTAGCAAAGTCGAGATGAATGTGAATATGAAGTATCAGCTCCAACTTCACCGCGG
AACACCCATCCAGAATGTCATTCTACATGAGCATCACATTTCTTGGTCCACTAACTACATTTATGTT
TAAATGAGGAAGACCTTCAGAAGGTTGCTGAGTACAAGACTGGGCTGTGCTGGAACACCCAGATTGTTCC
CATGTCAGGACTGCAGCAGCAAAGCCAATTTCAGGAGGTGTTGGAAAGATAACATCAACATGGCTCTAG
TTGTCGACACCTACTATGATGATCAACTCATTAGCTGTGGCAGCGTCAACAGAGGGACCTGCCAGCGACATG
TCTTCCCCACAATCATACTGCTGACATACAGTCGGAGGTTCACTGCATATTCTCCCCACAGATAGAAGAGC
CCAGCCAGTGTCTGACTGTGTGGTGAGCGCCCTGGGAGCCTACAGTCCTTCACTGTAAAGGACCGGTTCA
TCAACTCTTGAGGCAATACCATAATTCTTCTTACAGATCATCATTGCAATTGATATCAGTGA
GAAGGCTAAAGGAAAGCAAAGATGGTTTATGTTTGACGGACCAGTCCTACATTGATGTTTACCTGAGT
TCAGAGATTCTTACCCCATTAAAGTATGTCATGCCATTGAAAGCAACAATTTCAGTCATGTTGACGGTCC
AAAGGGAAACTCTAGATGCTCAGACTTTCACACAAGAATAATCAGGTTCTGTCATAAAACTCTGGATTGC
ATTCCTACATGAAATGCCCTGGAGTGTATTCTCACAGAAAAGAGAAAAAGAGATCCACAAAGAAGGAAG
TGTAAATATACTTCAGGCTGCGTATGTCAGCAAGCCTGGGGCCAGCTGCTAGACAAATAGGAGCCAGCC
TGAATGATGACATTCTTCCGGGTGTTGCAACAGCAGATTCTGCCAACCAATGGATCGATCTG
CCATGTCGACATTCTTCCCTATCAAATATGTCACAGACTCTTCAACAAGATGTCACACAAAACAATGTGAGAT
GTCTCCAGCATTTCAGGACCAATCATGAGCACTGCTTAATAGGACACTCTGAGAAATTGATCAGGCT
GTGAAGCGCGCCGTGATGAATATGCAACAGAGTTACACAGCTTGTGAGCGCGTGTGACTTATTCATGGGTC
AATTCAAGCGAAGTCCTTAAACATCTATATCCACCTTCATTAAGGAGACCTCACCATAGCTAATCTGGGA
CATCAGAGGGTCGCTTCATGCGAGGTTGTTGATCAGGACCATCAACCCCTCATGTGAATTCTC
TGGACTCCCATTCCAGTGTCTCCAGAAGTGATTGTGGAGCATACATTAAACCAAAATGGCTACACACTGGTTA
TCACTGGGAAGAAGATCACGAAGATCCATTGAAATGGCTGGGCTGCAGACATTCCAGTCAGTCAT
GCCTCTCTGCCACCCCTTGTTCAGTGTGGCTGGGCCAGACAAATGTCAGCGATGGAGGAATGCC
GCGGGACATGGACTCAACAGATCTGCTGCCAGTCATCACAGGTTCCAAATAGTCACCCCTTGAAAG
GAGGGACAAGGCTGACCATAATGTCAGGCTGGACATTGGATTCGGAGGAATAAAATTGATTTAAAGAAAA
CTAGAGTTCTCTGGAAATGAGAGCTGCACCTTGACTTAAAGTGAGAGCAGCATGAAATACATTGAAATGCA
CAGTTGGTCCTGCCATGAAATAAGCATTCAATATGTCATAATTTCAAATGGCACGGACAACACAAT
ACAGTACATTCTCTATGTGGATCCTGTAATAACAAGTATTCGCGAAATACGGTCTATGGCTGGTGGCA

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TABLE 27-continued

MET variant (with non-coding exon 27) Nucleotide Sequence (4651 nt, SEQ ID No. 65)

CTTTACTTAACTGGAAATTACCTAACAGTGGATTCTAGACACATTCAATTGGTGGAAAAACAT
 GTACTTTAAAAGTGTCAAACAGTATTCTGAATGTTACCCAGCCCCAACATTCAACTGAGTTG
 CTGTTAAATTGAAAATTGACTTAGCCAACCAGAGACAAGCATCTCAGTACCGTGAAGATCCCATTGTCT
 ATGAAATTCCATCCAACCAAATCTTTATTAGTACTGGTGGAAAGAACCTCTCAACATTGTCAGTTTCTAT
 TTGCTTGCCAGTGGTGGAGCACAATAACAGGTGTTGGAAAAACCTGAATTTCAGTTAGTGTCCCGAGAA
 TGGTCATAAATGTGCATGAAGCAGGAAGGAACTTACAGTGGCATGTCAACATCGCTTAATTCAAGAGATAA
 TCTGTTGACCACCTTCCCTGCAACAGCTGAATCTGCAACTCCCCCTGAAAACCAAAGCCTTTTCATGT
 TAGATGGGATCCTTCAAATACTTGATCTCATTATGTACATAATCCTGTTAAGCCTTTGAAAAGC
 CAGTGATGATCTCAATGGCAATGAAAATGTACTGGAAATTAAGtqggcqactqqcaattcqggcq
attatttatqatcatqgttcaatattttcatacttcattttcttatqatqagagqaaqc
aaggcataagagaatattgttqgtcagcaatctaactctttatcaatacqtaaqttqatca
cattaaaacttctacccotcagccaggcacqgtactacqtaatcccacqacttqggqg
qccaqqcgqgtqaatcactqgqatcaggqgatqcaaqaccqccqctqgccaatqgtqaaacc
catctccactaaaaataaaaaattaqctqgqcatqgtqgtqccctqtaatcccaqctactc
acqgqgtcqgqgqacqgqgtqactqgqatqccqaaqqcqgqgatqgactqgccaagatqgca
ccactgactGGAAATGATATTGACCTGAAGCAGTTAAAGGTGAAGTGTAAAAGTTGAAATAAGAGC
 TGTGAGAATATACTACATTCTGAAGCCGTTTATGCACGGTCCCAATGACCTGCTGAAATTGAACAGC
 GAGCTAAATATAGAGTGGAGCAAGCAATTCTCAACCGTCTGGAAAGTAATAGTTCAACCAGATCAG
 AATTTCACAGGATTGATTGCTGGTGTCTCAATATCAACAGCACTGTTATTACTACTGGGTTTCTG
 TGGCTGAAAAGAGAAAAGCAAAATTAAAGATCTGGCAGTGAATTAGTCGCTACGATGCAAGAGTACACACT
 CCTCATTGGATAGGCTTGTAAAGTGCCGAAGTGTAAAGCCAACTACAGAAATGGTTCAAATGAATCTGTA
 GACTACCGAGCTACTTCCAGAAGATCAGTTCTAATTCTCAGAACGTTCATGCCGACAAGTCAG
 TATCCTCTGACAGACATGCCCCCATCTAACTAGTGGGACTCTGATATATCCAGTCATTACTGCAAAT
 ACTGTCCACATTGACCTCAGTGTCTAAATCCAGAGCTGGCCAGGCAGTCAGCATGTAGTGTGATTGGGCCC
 AGTAGCCTGATTGTGCATTCAATGAAGTCATAGGAAGAGGGCATTGGTTGTATATCATGGACTTT
 TTGGACAATGATGGCAAGAAAATTCACTGTGCTGTAAAGTCTTACAGAATCAGACATAGGAGAAGTT
 TCCCAATTCTGACCGAGGGAACTCATGAAAGATTTAGTCATCCAAATGCTCTCGCTCTGGGAAATC
 TGCTGCGAAGTGAAGGGCTCCGCTGGTGGCTTACCATACATGAAACATGGAGATCTCGAAATTCTATT
 CGAAATGAGACTCATAATCCAACGTAAAAGATCTTATTGGCTTGGCTTCAAGTAGCCAAAGGCATGAAA
 TATCTGCAAGCAAAAGTTGTCACAGAGACTGGCTGCAAGAAACTGTATGCTGGATGAAAATTCA
 GTCAAGGGTTGCTGATTTGGCTTGCCAGAGACATGTATGATAAGAATACTATAGTGTACACAACAAACA
 GGTGCAAAGCTGCCAGTGAAGTGGATGGCTTGGAAAGTCTGCAAACCTCAAAGTTACCAAGTCAGAT
 GTGTGGTCTTGGCTGCTCTGGAGCTGATGACAAGAGGAGCCCCACCTTATCCTGACGTAAACACC
 TTTGATATAACTGTTACTGTTGCAAGGGAGAAGACTCCTACAAACCGAATACTGCCAGACCCCTTATAT
 GAAGTAATGCTAAATGCTGGCACCCCTAAAGCCGAAATGCGCCCATCCTTCTGAACTGGTGTCCCGATA

TABLE 27-continued

MET variant (with non-coding exon 27) Nucleotide Sequence (4651 nt, SEQ ID No. 65)

TCAGCGATCTTCTACTTTCATGGGGAGCAGTGTCCATGACGCTACTTATGTGAACGTAAAATGT
GTCGCTCCGTATCCTCTCTGTTGTCAAGAGATAACGCTGATGAGGTGGACACAGACCAGCCTCC
TTCTGGGAGACATCATAG

(Exon 27 is indicated as double underline.)

TABLE 28

Primer across the junction between MET exon 26 and 28

Primer across the junction CTGGAAATTAAAGGGAAATG between MET exon 26 and 28 (SEQ ID No. 61):

(Double underline indicates bases bordering the splice junction)

TABLE 29

sirRNA for selectively knockdown MET full length and variants expression

sirRNA targeting splice junction between MET exon 26 and exon 28

Sense (SEQ ID No. 63) 5' GUACUGGAAAUUAAGGGAdTdT 3'

TABLE 29-continued

15 sirRNA for selectively knockdown MET full length and variants expression

20 Antisense (SEQ ID No. 64) 3' dTdTCAUGACCUUUUUUCC-CUU (5'-P) 5'

25 siRNA targeting non-coding MET exon 27

30 Sense (SEQ ID No. 68) 5' CAGCAAUCUAACUUUUUdTdT 3'

Antisense (SEQ ID No. 69) 3' dTdTGUCGUUAGAUUGAGAA-AUA (5'-P) 5'

(Double underline indicates bases bordering the splice junction)

35

TABLE 30

NF1 (full length) Nucleotide Sequence (8520 nt, SEQ ID No. 70)

ATGGCCGCGCACAGGCCGGTGAATGGGTCCAGGCCGTGGTAGCCGCTTCGACGAGCAGCTCCAATAA
AAACAGGACAGCAGAACACACATACCAAAAGTCAGTACTGAGCACAAACAAGGAATGCTAATCAATATTTC
CAAATACAAAGTTTCTTGTTATAAGCGGCCCTCACTACTATTTAAAGAATGTTAACATATGAGAATA
TTGGAGAAGCTGCTGAAAAAAATTATCTCTCAGTTGATTATATTGGATAACTGGAAAAATGTC
TTGCTGGCAACCAAAAGGACACAATGAGATTAGATGAAACGATGCTGGTCAAACAGTTGCTGCCAGAAAAT
CTGCCATTTCACCTGTGTAAGGAAACAGCATGCAGCTGAACCTCGGAATTCTGCCCTCTGGG
GTTTATTTCTCAGCTGAAACAACCTCAATGCACTGCTTTAGTCGCAATTCTACCAAGGTTACAGGAAT
TAACTGTTGTTAGAAGACAATGTTGATGTTCATGATATAGAATTGTTACAGTATATCAATGTTGATTG
TGCAAAATTAAACGACTCCTGAAGGAAACAGCATTAAATTAAAGCCCTAAAGAAGGTTGCGCAGTTA
GCAGTTATAAATAGCCTGGAAAGGCATTTGGAAACTGGGTAGAAAATTATCCAGATGAATTACAAAAC
TGTACCAAGATCCCACAGACTGATATGGCTGAATGTCAGAAAAGCTATTGACTTGGTGGATGGTTTG
TGAAAGCACCAACGTAAGCAGCAGTTGGCCACTACAAATCATTCTCCTATCTGTGTCAGAAATA
ATCCAGGATATACCAAAGACGTGGTTGATGAAAACAACATGAATAAGAAGTATTCTGGACAGTCTAC
GAAAAGCTTGCTGGCATGGAGGAAGTAGGCAGCTGACAGAAAGTGTGCAATTGCTGTGCAAAC
GTGTAAGCAAGTACTTACATCAATTGGAGATAACTCTGTCAATTCCACTTTGTTCAGTCCATGGTG

TABLE 30-continued

NF1 (full length) Nucleotide Sequence (8520 nt, SEQ ID No. 70)

GTT GATCTTAAGAACCTGCTTTAATCCAAGTAAGCCATTCTCAAGAGGCAGTCAGCCTGCAGATGTGG
 ATCTAAATGATTGACTGCCTGTTCTCGTATAAGCCCTCACAAACAACACTTAAAGATCTG
 CCTGGCTCAGAATTACACCTCTACATTCACATGTGCTGGTAAATTCACTCCATCGAATCATCACCAAT
 TCCGCATTGGATTGGTGGCTAAGATTGATGCTGTGTTGACTCGGTTGAACCTCGAAATATGTTG
 GTGAAAACACTTCATAAAGCAGTCAAGGTTGGAGCACACCCAGCAATACGAATGGCACCGAGCTTAC
 ATTTAAAGAAAAAGTAAACAAGCCTTAAATTAAAGAAAAACCTACAGACCTGGAGACAAGAAGCTATAAG
 TATCTTCTCTTGCCATGGTAAACTAATTGATGAGATCCAAAGCTTGTGTTGAACTCCAAGAAAAC
 AGGGGCCGAAACCCAAGGCAGTACAGCAGAATTAAATTACAGGGCTCGTCCAACTGGTCCCTCAGTCACA
 CATGCCAGAGATTGCTCAGGAAGCAATGGAGGCTCGTGTCTTCATCAGTTAGATAGCATTGATTG
 TGGAAATCCTGATGCTCTGTAGAAACATTTGGGAGATTAGCTCACAAATGCTTTTACATCTGCAAGA
 ATTAACTAGTCATCAAATGCTTAGTAGCACAGAAATTCTCAAGTGGTGCAGGAAATATTGATCTGAG
 GAATAAAATTCTCTTAAATAAGCAGGCAGATAGAAGTTCTGTCACTTCTCTTTTACGGGTA
 GGATGTGATATTCCCTCTAGTGGAAATACCAGTCAAATGTCCATGGATCATGAAAGAATTACTACGTACTC
 CTGGAGCCTCTCCGGAAAGGGAAAGGGAAACTCCTCTATGGATAGTGCAGCAGGATGCAGCGAACCC
 CCCGATTGCCGACAAGCCCAGACCAAACTAGAAGTGGCCCTGTACATGTTCTGTGAAACCTGACACT
 GAAGCTGTTCTGGTGCATGCTGTTCCGCCACCTCTGTGAGGAAGCAGATATCCGGTGTGGGTGG
 ATGAAGTGTCACTGCATAACCTTGTGCAACTATAACACATTGAGGTTGCTCTGTGCAAAAT
 GATGTCACACAGGAAGAGCAGCAGTCAGAAAAGAGTGTGGCACTGCTGAGGCGCATTGAGCATCCC
 GCAGGAAACACTGAGGCTGGGAAGATAACATGCAAATGGAAACAAGCAACAAAGCTAACCTTAAC
 ATCCAAAAGC AAAATGGAAGATGCCAGGCTGCTGAAAGCCTCACAAAGACATTGTTAAGAGGCGAAT
 GTCCCATGTGAGTGGAGGAGATCCATAGATTGTCAGCACAGACTCCCTACAGGAATGGATCAACATG
 ACTGGCTCTTGTGCCCTGGGGAGTGTGCCCTCAGCAGAGAAGCAATTCTGCCCTGCCAACCTATA
 GCCCACCCATGGGTCCAGTCAGTGAACGTAAGGGTCTATGATTTCACTGATGTTGCTCAGAGGGAAACGC
 AGATACACCTGTCAGCAAATTATGGATCGGCTGTTGCTTAATGGTGTGTAACCATGAGAAAGTGG
 CTTCAAATACGGACCAATGTTAAGGATCTGGGGCTAGAATTGAGTCAGTGTGCTGTATCAAATGCTAT
 TTAACAAATTGAGAAATACCATCAGCAAGTTTTGACTCCAAAGGACAGGTTTATTGACTGATACCAA
 TACTCAATTGAGAAACAAACCATGCTATAATGAGAAACTTGCTAGATAATCAGACTGAAGGCGCT
 GAACATCTAGGGCAAGCTAGCATTGAAACAATGATGTTAAATCTGGTCAGGTATGTTGCTGTGCTGG
 ATATGGTCCATGCAATTCAAATAAAACGAAACTGTTGCAATTAGTTGAGTAATGATGGCAAGGAGAGA
 TGACCTCTCATTGCAAGAGATGAAATTAGGAATAAGATGGTAGAAACCTGACAGACTGGTTATG
 GGAACATCAAACCAAGCAGCAGATGATGTTAAATGCTTACAAGAGATTGGACCAGGCAAGCATGG
 AAGCAGTAGTTCACTCTAGCTGGCTCCCTCTGCAGCCTGAAGAAGGAGATGGTGTGAAATTGATGGA
 AGCCAAATCACAGTTATTCTTAAACTTCACATTATGAACTTGTGACTGAGCTGAGTT
 GAAGATGAAAGTGCACAAACAGGTGGCAGGAAACGTGGCATGTCGGAGGCTGGCATCACTGAGGCACT
 GTACGGTCTGCAATGCAAACTTACTCAATGCCAACGTTAGACAGTGGTCTCATGCACTCCATAGGCTT
 AGGTTACCAAGGATCTCCAGACAAGAGCTACATTGAACTTGTGACAAAAATCCTCAACAAGGC
 ACAGAATTGACACACTGCAAGAAACAGTATTGGCTGATGGTTGAGAGATTGGTGGACTGGTCACAA
 TGATGGGTGATCAAGGAGAACTCCCTATAGCGATGGCTCTGCCAATGTTGCTTGTGTTCTCAGTGG
 TGAACACTGCTGAGTTCTGGTTACTCTGTTGATTCTGGCATTACTCTACCAACTGCTCTGGAACATG

TABLE 30-continued

NF1 (full length) Nucleotide Sequence (8520 nt, SEQ ID No. 70)

TTTCTAAAGAAGTAGAATTGGCAGACTCCATGCAGACTCTTCGAGGCAACAGCTGGCAGTAAAA
 TAATGACATTCTGTTCAGGTATATGGTCTACCTATCTACAAAACCTGGATCCTTATTACGAAT
 TGTGATCACATCCTCTGATTGGCAACATGTTAGCTTGAGTTGGATCCTACCAGGTAGAACCATCAGAG
 AGCCTTGAGGAAACACAGCGGAACCTCCTCAGATGACTGAAAAGTTCTCCATGCCATCATCAGTCCT
 CCTCAGAATTCCCCCTCAACTCGAAGTGTGCCACTGTTATACCAGGCAACTTGCCACTCCCTACT
 GAATAAAGCTACAGTAAAAGAAAAAGGAAAACAAAAATCAGTGGTAGCCAGCGTTCCCTCAGAAC
 AGCATCGGTGCAGTAGGAAGTGCATGTTCTCAGATTATCAATCCTGCCATTGTCACCGTATGAAG
 CAGGGATTTAGATAAAAGCCACCACCTAGAATCGAAAGGGCTGAGTTAATGTCAGAACATTC
 GAGTATTGCCATCATGTTCTCAGAAAAGAACATATGCCCTTCAATGATTTGTGAAAAGC
 AACTTTGATGCAGCACGAGGTTTCTGATAGCATCTGATTGTCACAAGTGATGCAGTAATC
 ATAGTCCTTCCTCATAAGTGACGGCAATGTGCTTACATCGTCACTCTGGAACAAATCAGGAGAA
 AATTGGCAGTATCTTCCAGAACAGGGATCATAAGCTGTTGAAAGACGACCTTTGATAAGATGGCA
 ACACCTCTGCATACTGGTCTCCAGAGCACAAACCTGTGGCAGATACACACTGGTCCAGCCTAAC
 TTACCAAGTCAAAGTTGAGGAAATTATGACTAGGCATCAGGTACATGAAAAGAACATTCAAGGCTT
 GAAAAGCTTAAGTATTTCTACCAAGCTGGACTTCCAAGCTGGAAATCTATTTTTATTATGTTGCA
 CGGAGGTTCAAACCTGGTCAAATCAATGGTGAATTGCTGATATACCATGTCCTACTGACTTTAAC
 ATTATGCAAAGCCATATGAAATTGAGTGGACCTTACCCATACGGGCTAGCAATCGCTTAAACAGA
 CTTCTCTCTAAGTGGTTGTTGTTCTGGCTTGCTTACGACAACGCTCCAGTCTATCTAT
 ACTGTAACCTGGGTAGGGAGTACACCAAGTATCATGAGCGGCTGCTGACTGGCTCAAAGGTAGCA
 AAAGGCTTGTTCATAGACTGCTGGAAACTGGCTGAGCACATAGAGCATGAAACACAGAAACTACC
 TGCTGCCACCTGGTTAGAAGAGGACCTGAAGGTATTCCACATGCTCAAGCTCAGTCACAAAGAC
 ACCAAAGTTCTATTAAAGTGGTTACTGCTGTCAAAGTAACCTCAGCAGAGGAAACAAAGCTTAG
 GGCACATGCTTCTAAATGACATTATTGCTCGGAAATGAGAAATCTGCTTAGAGATGAGAA
 CCAGTTCACCTAACCATGCAAACCCAGGGCACGCCGTCACCTCATGCACCCAGGAGTGTGAAGCCATT
 GTCCAGTCTATCATATCCGACCGCTGGAACTGTCACAGCCCAGTCTATCCCCAACACACCA
 AGATTGGCCTAAAGATGTCCTGGACACTGCTCAATATGCCATTACTTAATTAGGAGTTCTGACCC
 GAGTTACGGTCAGTGCCTATAATCTCTGTGCTTAACTGTACCTTAATTAAAATCGAGGGC
 CAGTTACTAGAGACATCAGGTTATGTATCCGTGCAACAAACACCCCTTTATTGCTCTATTAGTAAGA
 CACTGGCAGCCAATGAGCCACACCTCACGTTAGAATTGGAAAGAGTGTATTCTGGATTAGCAAATC
 TAGTATTGAATTGAAACACCTTGTGAAATACATGACTCCATGGCTGTCAAATCTAGTTGTTTGC
 AACGATAATGATGATGCCAACAGACAAAGAGTTACTGCTATTCTGACAAGCTGATAACAATGACCA
 ATGAAAACAGATGTACCCATCTATTCAAGAAAAATATGGGAAGCCTGGCAGATTACAGATCTGCT
 TGATGTTGACTAGACAGTTCATCAAACACAGTGCACACAGGGCTGGATCAATAAGCTGAGGT
 ATGGCAGATACTGCTGTAGCTTGGCTCTGGAAATGTGAAATTGGTTCAAGCAAGGTTATGGAAGGA
 TGTGCAAATAATTGACAAGACATGCTTATCTCAACTCCTACTTGAACAAACATCTTATGTTGGATGA
 TATTGCTATTAGCACGCTACATGCTGATGCTGTCTCAACAAATTCCCTGATGTGGCAGCTCATCTT
 CCCTACCTCTTCCACGTTGTTACTTCTAGTAGCCACAGGTCGCTCTCCCTAGAGCTCCACACATG
 GACTGGTCATTAATATCATTCACTCTGTGACTTGTGTTCAAGCTCATTAGTGAAGAGACCAAGCA
 AGTTTGAGACTCAGTCTGACAGAGTTCTCATACCCAAATTCTACTTGCTGTTGGCATTAGCAAAGTC

TABLE 30-continued

 NF1 (full length) Nucleotide Sequence (8520 nt, SEQ ID No. 70)

AAGTCAGCTGCTGTCAATTGCCCTCCGTTCCAGTTACCGGGACAGGTCAATTCTCTGGCTCTATGAGA
 GAGAGACTTTGCTTGACATCCTGGAAACAGTCACAGAACAGCTTGGAGATCATGGAGGCATGCAT
 GAGAGATATTCCAACGTGCAAGTGGCTGGACCAGTGGACAGAACAGCTCAAAGATTGCATTCCAATAT
 AATCCATCCCCTGCAACCAAGAGCTTGTGTTGCTTGGGTGATTAGCAAACAGAGTGTCTCATGGCAGA
 TAAAGCAGATAATCCGTATTCTAGCAAGGCACTTGAGAGTTGCTAAAAGGACCTGACACTTACAACAG
 TCAAGTTCTGATAGAACAGCTAACAGTAATAGCACTAACCAAATTACAGCCACTTCTTAATAAGGACTCGCCT
 CTGCACAAAGCCCTTTGGTAGCTGTGGCTGTGAGCTTGATGAGGTCAACTGTATTAGCAG
 GTACCGCAGTCTTGAAACAAACCTGCATACTTAGATAGTCTCCGTATATTCAATGACAAGAGTCCAGA
 GGAGATTTATGGCAATCCGAATCCTCTGGAGTGGCACTGCAAGCAAATGGATCTTTGGACTC
 AATTCAACTCTAACCTTAACTTGCAATTGGTGGACACCTTAAAAGGTACAGGCATCTCACCTG
 CTATTGTTGCAAGAACAGTCAGAACATTACATACACTAACACTCTGGTAAACAAACAGAACATTGTGA
 CAAATTGAGTGAATCACAGAGCTGGCTACTTAGCAGCTTACTACAGTGTGAAGAACAGTCGA
 AGTCGCTGCAGCCTAAACATAGAACAGTCACCTCTTACTGATATTCAATGGAAATGTTCTATGG
 ATACATATCCCATTACATCATGGTGAACCTTCTTACAGAACACTAAAGGAGACTCAGCCATGGTCTCTCC
 CAAAGGTTCTGAAGGACACCTTGCAAGCCACCTATCAAACACTGTCGGCCAGACCAGTCCCCGAGGCCAGGAAA
 TCCATGAGCCTGGACATGGGCAACCTCTCAGGCCAACACTAAGAACAGTTGCTGGAAACAGGAAAAGTT
 TTGATCACTTGATATCAGACACAAAGGCTCTAAAGGCAAGAACATGGAAATCAGGGATCACACACCCCC
 CAAAGGAGAGTAGCAGAACACTGATTGAAATGGAAACTCAGAGGATTCTCATCACACAGCAC
 CCACATTTACGTAAAGTTCTAGTGTGAATCAAATGTTCTTGGATGAAGAACAGTACTACTGATCCGA
 AGATCCAGGCGCTGCTTACTGTTCTAGTACACTGGAAAAATACACAGATGAGTTGATCAACG
 ATTCTTATGAATACTTAGCAGAGGCCAGTGTGTTCTCAAAGTCTTCTGTGCTGATAATTG
 TTGGAACAGTGTGGTACCATGAAGAACCTCCACCAATACCAACATCTTACCTGCAAAGTTGG
 TTTAATGGCTTGCGGTTGCAGGACCGTTCAAAGCAAACACAAATTCCAGACTATGCTGAGCTT
 ATTGTTAAGTTCTTGATGCCCTGATTGACACGTACCTGCCTGGAATTGATGAAGAACAGTGAAGAAT
 CCCTCCTGACTCCCACATCTCCTTACCTCCTGCACAGGCCAGCTTAGTATCACTGCCAACCTTAA
 CCTTCTAACTCCATGACCTACTGCAACTTCCAGCATTCCCAGGAATCGACAAGGAGAACGTTGAA
 CTCTCCCTACCAACTGGCACTGTAACAGTGGACACTGCCACGGATCGCAAGCCAAGTGCAGAACG
 AAAAGAGCGCTGGCAGTTCAAACGTAATAGCATTAAGAACAGATCGTGTGA

(Exon 8 is indicated as double underline.)

TABLE 31

 NF1 variant (lacking exon 8) Nucleotide Sequence
 (8444 nt, SEQ ID No. 76)

ATGGCCGCGCACAGGCCGTGGAATGGTCCAGGCCGTGGTCAGCCGCTCGACGAGCAGCTCCAATAA
 AACACAGGACAGCAGAACACACATACCAAAGTCAGTACTGAGCACAAACAAAGGAATGTCTAAATCAATATT
 CAAATACAAGTTCTTGTTATAAGCGGCCACTACTATTAAAGAACATGTTAACAAATGAGAATA
 TTTGGAGAACAGTGTGAAAAAAATTATCTCTCAGTTGATTATATTGGATAACTGGAAAAATGTC
 TTGCTGGCAACCAAGGACACAAATGAGATTAGATGAAACGATGCTGGCAAACAGTTGCTGCCAGAAAT

TABLE 31-continued

NF1 variant (lacking exon 8) Nucleotide Sequence (8444 nt, SEQ ID No. 76)
CTGCCATTTCTCACACCTGTCGTGAAGGAACCAAGCATGCAGCTGAACCTCGGAATTCTGCCCTGGG GTTTATTTCTCAGCTCAACAACCTCAATGCAGCTTTAGTCGCATTTCTACCAGTTACAGGAAT TAACTGTTGTTCAGAAGACAATGTTGATGTTCATGATATAGAATTGTTACAGTATATCAATGTGGATTG TGAAAATTAAACGACTCCCTGAAGGAAACAGCATTAAATTAAAGCCCTAAAGAAGGTTGCGCAGTTA GCAGTTATAAA <u>TAGCCTGGAAAAGAATGTGCA</u> AGAAAGCTATTGACTTGGTGGATGGTTTGCTGAAAG CACCAACAGTAAAGCAGCAGTTGCCACTACAAATCATTCTCCTTATCTTGTGTCAGAAATAATCCAG GATATATCAAAGACGTGGTGTGATGAAAACACATGAATAAGAAGTTATTCTGGACAGTCTACGAAAAG CTCTGCTGCCATGGAGGAAGTAGGCAGCTGACAGAAAGTGCCTGCAATTGCCATGTGTCAGAACTGTGAA ACCAAGTACTTACATCAATTGGAAAGATACTCTGCAATTCCCTACTTGTGCTCCATGGTGGTTGAT CTTAAAGAACCTGCTTTAATCCAAGTAAGCCATTCTCAAGAGGCAGTCAGCCTGCAGATGTGGATCTAA TGATTGACTGCCTTGTGTTCTGCTTCGTATAAGCCCTCACACAAACACATTAAAGATCTGCCCTGGC TCAGAATTCACCTCTACATTCACTATGTGCTGGTAAATTCACTCCATCGAATCATCACCAATTCCGCA TTGGATTGGTGGCCTAAGATTGATGCTGTGTTGCACTCGGTTGAACCTCGAAATATGTTGGTGAAGA CACTTCATAAAACAGTGCAGGTTGAGCACACCCAGCAATACGAATGCCACCGAGTCTTACATTAA AGAAAAAGTAACAAGCCTTAAATTAAAGAAAAACCTACAGACCTGGAGACAAGAAGCTATAAGTATCTT CTCTGTCCATGGTGAACACTATTGATGCAAGATCCAAGCTTGTGTTGTAATCCAAGAAAACAGGGGC CCGAAACCCAAGGCAGTACAGCAGAATTAAATTACAGGGCTCGTCCAACTGGTCCCTCAGTCACACATGCC AGAGATTGCTCAGGAAGCAATGGAGGCTCTGCTGGTTCTCATCAGTTAGATAGCATTGATTGTGGAAT CCTGATGCTCCTGTAGAACATTGGGAGATTAGCTCACAAATGCTTTTACATCTGCAAGAAATTAA CTAGTCATCAAATGCTTAGTAGCACAGAAATTCTCAAGTGGTGCAGGAAATTGATCTGCAGGAATAA ATTCTCTTAAATAAGCAGGCAGATAGAAGATTCTGTCACTTCTCCTTTACGGGTAGGATGT GATATTCTCTAGTGGAAATACCAGTCAGTCAATTGTCCATGGATCATGAAGAATTACTACGTACTCCTGGAG CCTCTCTCGGAAGGGAAAGGGAACTCCTCTATGGATAGTGCAGCAGGATGCAGCGGAACCCCCCGAT TTGCCGACAAGCCCAGACCAACTAGAAGTGGCCCTGTACATGTTCTGTGGAACCTGACACTGAAGCT GTTCTGGTTGCCATGTCCTGTTCCGCCACCTCTGTGAGGAAGCAGATATCCGTGTGGGGTGGATGAAG TGTCAGTCATAACCTCTGCCAACTATAACACATTGAGTTGCCTCTGTGAGCAATATGATGTC AACAGGAAGAGCAGCACTTCAGAAAAGAGTGTGGCACTGCTGAGGCGCATTGAGCATCCACTGCAGGA AACACTGAGGCTGGAGATAACATGCAAAATGGAAACAGCAACAAAGCTAACCTTAACTATCCAA AAGCCAAATGGAAGATGGCAGGCTGCTGAAAGCCTCACAGGACATTGTTAAGAGGCAGATGTCCCA TGTGAGTGGAGGAGGATCCATAGATTGTCGACACAGACTCCCTACAGGAATGGATCACATGACTGGC TTCTTGTGCCCTGGGGAGTGTGCCCTCAGCAGAGAAGCAATTCTGCCCTGGCAACCTATAGCCCAC CCATGGGTCCAGTCAGTGAACGTAAGGGTTCTATGATTCAGTGTCTCAGAGGGAAACCGAGATAAC ACCTGTCAGCAAATTATGGATGGCTGTTGTCCTTAATGGTGTGTAACCATGAGAAAGTGGACTTCAA ATACGGACCAATGTTAAGGATGGTGGGCTAGAATTGAGTCCTGCTCTGTATCCAATGCTATTAAACA AATTGAGAATACCATCAGCAAGTTTGACTCCAAGGACAGGTTTATTGACTGATACCAAACTCA ATTGAGAACAACCATAGCTATAATGAAGAACTTGCTAGATAATCATACTGAAGGCAGCTCTGAACAT CTAGGGCAAGCTAGCATTGAAACAATGATGTTAAATCTGGTCAGGATGTTCTGTGCTGGGAATATGG TCCATGCAATTCAAATAAAACGAAACTGTCATTAGTGAAGTAATGATGGCAAGGAGAGATGACCT CTCATTGCAAGAGATGAAATTAGGAATAAGATGGTAGAATACCTGACAGACTGGTTATGGGAACA

TABLE 31-continued

NF1 variant (lacking exon 8) Nucleotide Sequence
(8444 nt, SEQ ID No. 76)

TCAAACCAAGCAGCAGATGATGATGAAAATGTCTTACAAGAGATTGGACCAGGAAGCATGGAAGCAG
TAGTTTCACTCTAGCTGGTCCCTCTGCAGCCTGAAGAAGGAGATGGTGTGGAATTGATGGAAGCCAA
ATCACAGTTATTCTTAAACTTCACATTATTATGAACCTTTGAATGACTGCAGTGAAGTTGAAGAT
GAAAGTGCGAACACAGGTGGCAGGAAACGTCGGCATGTCTCGGAGGCTGGCATCACTGAGGCAGTACGG
TCCTTGCAATGTCAAACCTACTCAATGCCAACGTTAGACAGTGGTCTCATGCACTCCATAGGCTTAGGTTA
CCACAAGGATCTCCAGACAAGAGCTACATTATGGAAGTTCTGACAAAAATCCTCAACAAGGCACAGAA
TTTGACACACTTGCAAGAACAGTATTGGCTGATCGGTTGAGAGATTGGTGGAACTGGTCACAATGATGG
GTGATCAAGGAGAACTCCCTATAGCGATGGCTCTGGCAATGTGGTCCCTGTTCTCAGTGGGATGA
AGCTCGAGTTCTGGTTACTCTGTTGATTCTGGCATTACTCTACCAACTGCTCTGGAACATGTTTCT
AAAGAAGTAGAAATTGGCAGACTCCATGCAGACTCTCTCCAGGCAACAGCTGGCAGTAAAATAATGA
CATTCTGTTCAAGGTATATGGTGACCTATCTACAAAAACTCTGGATCCTTATTACGAATTGTGAT
CACATCCTCTGATTGGCAACATGTTAGCTTGAAAGTGGATCCTACAGGTTAGAACCATCAGAGAGCCTT
GAGGAAACCGCGAACCTCTTCAGATGACTGAAAAGTCTCCATGCCATCATCAGTCCCTCCTCAG
AATTCCCCCTCAACTCGAAGTGTGCCCCACTGTTATACCAGGCAACTGCCACTCCCTACTGAATAA
AGCTACAGTAAAAGAAAAAGGAAAACAAAAAATCAGTGGTTAGCCAGCGTTCCCTCAGAACAGC
GGTGCAGTAGGAAGTGCATGTCCTCAGATTATCAATCCTGCCATTGTCACCGTATGAAGCAGGG
TTTAGATAAAAGCCACCACTAGAATCGAAAGGGCTTGAAGTTAATGTCAAAGATACTTCAGAGTAT
TGCCAATCATGTTCTTCACAAAAGAAGAACATATGCCCTTCAATGATTGTGAAAAGCAACTTT
GATGCAGCACCGAGGTTTCTTGATATAGCATCTGATTGCCCTACAAGTGTGAGTAAATCATAGTC
TTCCCTTCATAAGTGACGGCAATGTGCTTACATCGTCACTCTGGAAACATCAGGAGAAAATTGG
GCAGTATCTTCCAGCAACAGGGATCATAAAGCTGTTGGAAAGACGACCTTGATAAGATGCCAACACTT
CTTGCAACACTGGGCTCCAGAGCACAAACCTGTGGCAGATACACACTGGCCAGCCTAACCTTACCA
GTTCAAAGTTGAGGAATTATGACTAGGCATCAGGTACATGAAAAAGAAGAATTCAAGGTTGAAAAC
GTTAAGTATTTCTACCAAGCTGGACTTCCAAAGCTGGGAATTCTTATTATGTTGACGGAG
TTCAAAACTGGTCAAATCAATGGTGAATTGCTGATATACCATGTTACTGACTTTAAAGCCATATTATG
CAAAGCCATATGAAATTGAGTGGACCTTACCCATACGGGCTAGCAATCGCTTAAACAGACTTTCT
CTCTAAGTGGTTGTTGTTCTGGCTTACGACACAGCTCCAGTCAAGGTTAATCTATAACTGT
AACTCCTGGGTCAAGGAGTACACCAAGTATCATGAGCGGCTGCTGACTGGCCTCAAAGTAGC
TTGTTTCATAGACTGCTCTGGAAACTGGCTGAGCACATAGAGCATGAACAAACAGAAA
CAGTCTTCTAAATGACATTATTGCTTGGAAATTGAGAAACTGCTTAGTGAAGAACAGTT
CACCTTAACCATTGCAAACCAAGGGCACGCCCTCACCTTCATGCACCAGGAGTGTGAAGC
TCTATCATTCAATCCGGACCCGCTGGAACTGTCACAGCCCAGTCTATCCCCAACACACCAAGATT
GGCAGGAAAGATGCCCTGGACACTGCTCAATATGCATTACTTAATTAGGCAGTCTGACCCGAGTT
ACGGTCAGCTGCCTATAATCTCTGTGCTTAACTGTACCTTAATTAAAATGAGGGCCAGTTA
CTAGAGACATCAGGTTATGTATCCCTGCCAACAAACACCCCTTTATTGTCCTATTAGTAAGACACTGG
CAGCCAATGAGCCACACCTCACGTTAGAATTGGAAAGAGTGTATTCTGGATTAGCAAATCTAGTAT

TABLE 31-continued

NF1 variant (lacking exon 8) Nucleotide Sequence (8444 nt, SEQ ID No. 76)
TGAATTGAAACACCTTGTGGAAATACATGACTCCATGGCTGCAAATCTAGTCGTTTGCAAGCAT AATGATGATGCCAACGACAAAGAGTTACTGCTATTCTGACAAGCTGATAACAATGACCATCAATGAAA AACAGATGTACCCATCTATTCAAGAAAAATGGGGAAAGCCTGGGAGATTACAGATCTGCTTGTGATGT TGTACTAGACAGTTCATCAAACCAAGTGCAACAGGTGGCTGGATCAATAAGCTGAGGTGATGGCA GATACTGCTGTAGCTTGGCTCTGGAAATGTGAAATTGGTTCAAGCAAGGTTATTGGAAGGATGTGCA AAATAATTGACAAGACATGCTTATCCTAACACTTAACTGAAACAACATCTTATGTGGATGATATTGC TATTTAGCACGCTACATGCTGATGCTGTCCTCAACAATTCCCTGATGTGGCAGCTCATCTCCCTAC CTCTCCACGTTGTTACTTCTTAGTAGCCACAGGTCCGCTCCCTAGAGCTTCCACACATGGACTGG TCATTAATATCATTCACTCTGTGACTTGTACAGCTTCATTAGCTTATGAGGTTCAAGGAGACCAAGCAAGTTT GAGACTCAGTCTGACAGAGTTCTCATTACCCAAATTTACTTGCTGTTGGCATTAGCAAAGTCAAGTCA GCTGCTGTCATTGCTTCCGTTCCAGTTACCGGGACAGGTATTCTCTGGCTCTATGAGGAGAGA CTTTGCTTGACATCCTGGAAACAGTCACAGAAGCTTGTGGAGATCATGGAGGCATGCATGAGAGA TATTCCAACGTGCAAGTGGTGAGGACTGAGACTAGCTCAAAGATTGCAATTCAATATAATCCA TCCCTGCAACCAAGAGCTCTGTGCTTGGGTGATTAGCAAACGAGTGTCTCATGGCAGATAAGC AGATAATCCGTATTCTTAGCAAGGCATTGAGAGTTGCTTAAAGGACCTGACACTTACAACAGTCAAGT TCTGATAGAAGCTACAGTAATGCACTAACAAATTACAGCCACTCTTAATAAGGACTCGCCTCTGCAC AAAGCCCTCTTGGTAGCTGTGGCTGCTGAGCTTGTGAGGTCAACTTGATTCAAGGTTACCG CACTCTTGAAACAAACCTGCATACTTAGATAGTCTCGTATATTCAATGACAAGAGTCCAGAGGAAGT ATTATGGCAATCGGAATCCTCTGGAGTGGCACTGCAAGCAAATGGATCATTTGTTGGACTCAATT AACTCTAACTTAACTTGCAATTGGTGACACCTTTAAAGGGTACAGGCATCCTCACCTGCTATTG TTGCAAGAACAGTCAGAATTACATACACTAACTCTGGTTAACAAACACAGAAATTGTGACAAATT TGAAGTGAATACACAGAGCGTGGCTACTTAGCAGCTTACTTACAGTGTCTGAAGAAGTTCGAAGTC TGCAGCCTAAACATAGAAAGTCACTCTTCTACTGATATTCAATGGAAATGTTCTATGGATACAT ATCCCATTCATGGTGAACCTTCTAGGACACTAAAGGAGACTCAGGCATGGCTCTCCAAAGG TTCTGAAGGATACCTTGCAAGCACCTATCCAACTGTCGGCCAGACAGTCCCCGAGCCAGGAATCCATG AGCCTGGACATGGGCAACCTCTCAGGCCAACACTAAGAAGTTGCTGGAAACAAGGAAAGTTTGATC ACCTGATATCAGACACAAAGGCTCTAAAAGGCAAGAAATGGAATCAGGGATCACAACACCCCCAAAAT GAGGAGAGTAGCAGAAACTGATTATGAAATGAAACTCAGAGGATTTCCTCATCACACAGCACCCACAT TTACGTAAAGTTCTAGTGTGAATCAAATGTTCTTGGATGAAGAAGTACTTACTGATCCGAAGATCC AGGCCTGCTCTTACTGTTCTAGTACACTGGTAAATACCAACAGATGAGTTGATCAACGAATTCT TTATGAATACTTAGCAGAGGCCAGTGTGTTCCAAAGTCTTCTGTTGCTGATAATTGTTGGAC TCTAAGATCAACACCCCTGTTATCATTGTGCCAAGATCCAAATTGTTAAATCCAATCCATGGAATTGTG AGAGTGTGGTGTACCATGAAGAATCCCCACCAACACAAATCTTACCTGCAAAGTTGGTTAA TGGCTTGTGGCGGTTGCAAGGACCGTTCAAGCAAACACAAATTCCAGACTATGCTGAGCTTATTGTT AAGTTCTTGATGCCCTGATTGACACGTACCTGCCTGGAATTGATGAAGAACCAGTGAAGAATCCCTCC

TABLE 31-continued

NF1 variant (lacking exon 8) Nucleotide Sequence
(8444 nt, SEQ ID No. 76)

TGACTCCCACATCTCCTTACCCCTCCGCAGCTGCAGAGGCCAGCTTAGTATCACTGCCAACCTTAACCTTC
TAATTCCATGACCTCACTTGCAACTTCCCAGCATTCCCAGGAATCGACAAGGAGAACGTGAACTCTCC
CCTACCACGGCCACTGTAACAGTGGACGAACTGCCACGGATCCGCAAGCCAAGTGCAGAAGCAAAGAA
GCGCTGGCAGTTCAAAACGTAATAGCATTAAGAAGATCGTGTGA

(Double underline indicates bases bordering the splice junction)

TABLE 32

Primer across the junction between NF1 exon 7 and 9

Primer across the junction GCGCTGGAAAAGAAATGTGCGAGA
between NF1 exon 7 and 9
(SEQ ID No. 75)

(Double underline indicates bases bordering the splice junction)

TABLE 33

siRNA for selectively knockdown NF1 full length and variants expression

siRNA targeting NF1 exon 8

Sense (SEQ ID No. 73) 5' CCAGAUCCCACAGACUGAUdTdT 3'
Antisense (SEQ ID No. 74) 3' dTdTGUCUAGGGUGUCUGA-CUA (5'-P) 5'

siRNA targeting splice junction between NF1 exon 7 and exon 9

Sense (SEQ ID No. 77) 5' GGAAAAGAAUGUGCAGAAAdTdT 3'
Antisense (SEQ ID No. 78) 3' dTdTCUUUUUUACACGUC-UUU(5'-P) 5'

(Double underline indicates bases bordering the splice junction)

TABLE 34

BAK1 (full length) Nucleotide Sequence
(636 nt, SEQ ID No. 79)

ATGGCTTCGGGCAAGGCCAGGTCTCCAGGCAGGAGTGGGAGAGCC
TGCCCTGCCCTCTGCTTCTGAGGAGCAGGTAGCCAGGACACAGAGGAGG
GGGGTGGCTGCCCTGCCGACCCAGAGATGGTACACCTTACCTCTGCAACC
TAGCAGCACCATGGGCAGGTGGACGGCAGCTGCCATCATCGGGACG
ACATCAACCGACGCTATGACTCAGAGTCCAGACCATGTTGCAGCACCTG
CAGCCCACGGCAGAGAATGCCTATGAGTACTTCACCAAGATTGCCACCAG
CCTGTTGAGAGTGGCATCAATTGGGGCGTGTGGTGGCTCTCTGGGCT
TCGGCTACCGTCTGGCCCTACACGTCTACCAGCATGGCCTGACTGGCTC
CTAGGCCAGGTGACCCGCTTCTGTTGACTTCATGCTGCATCACTGCAT
TGCCCCGGTGGATTGCACAGAGGGTGGCTGGGTGGCAGCCCTGAACCTGG

15

BAK1 (full length) Nucleotide Sequence
(636 nt, SEQ ID No. 79)

20

GCAATGGTCCCACCTGCACAGTGTGGTGGCTGGGTGTTCTGTTG
GGCCAGTTGTGGTACGAAGATTCTCAAATCATGA

(Exon 2 is indicated as double underline.)

TABLE 35

BAK1 variant (lacking exon 2) Nucleotide Sequence (501 nt, SEQ ID No. 85).

ATGGCTTCGGGCAAGGCCAGGTCTCCAGGCAGGAGTGGGAGAGCC
TGCCCTGCCCTCTGCTTCTGGGCACCATGGGCAGGTGGGACGGCAGCTCG
CCATCATCGGGACGACATCAACCGACGCTATGACTCAGAGTCCAGACC
ATGTTGCAGCACCTGCAGCCCACGGCAGAGAATGCCTATGAGTACTTCAC
CAAGATTGCCACCAGCCTGTTGAGAGTGGCATCAATTGGGGCGTGTGG
TGGCTCTCTGGGCTTCGGCTACCGTCTGGCCCTACAGTCTACCAGCAT
GGCCTGACTGGCTTCCTAGGCCAGGTGACCCGCTTGTGGTCGACTTCAT
GCTGCATCACTGCATTGCCGGTGGATTGCACAGAGGGTGGCTGGTGG
CAGCCCTGAACTTGGCAATGGCCCACCTGAAACGTGCTGGTGGTTCTG
GGTGTGGTCTGTTGGCCAGTTGTGGTACGAAGATTCTCAAATCATG

35

40

45

A

(Double underline indicates bases bordering the splice junction)

TABLE 36

Primer across the junction between BAK1 exon 7 and 9

Primer across the junction TCTGCTTCTGGCACCATGG
between BAK1 exon 1 and 3
(SEQ ID No. 84)

50

55

(Double underline indicates bases bordering the splice junction)

TABLE 37

sirRNA for selectively knockdown BAK1 full length and variants expression

sirRNA targeting exon 2

Sense (SEQ ID No. 82) 5' GGUCACCUUACCUCUGCAAdTdT 3'

60

65

TABLE 37-continued

siRNA for selectively knockdown BAK1 full length and variants expression	
Antisense (SEQ ID No. 83) 3'	dTdTCCAGUGGAUAGGAGAC-GUU(5'-P)5'
siRNA targeting splice junction between exon 1 and exon 3	
Sense (SEQ ID No. 86) 5'	CCCUCUGCUUCUGGCACCAdTdT
Antisense (SEQ ID No. 87) 3'	dTdTGGAAGACGAAGACGU-GGU (5'-P)5'

(Double underline indicates bases bordering the splice junction)

Methods of Detection

The present invention provides a method of identifying splicing variants of genes associated with prostate cancer risk and survival. The method generally comprises detecting the splicing variants in a nucleic acid sample from an individual, such as a prostate biopsy specimen. Typically, total RNA is extracted from the specimen, cDNA is synthesized from the extracted RNA and subject to further analysis. Nucleic acid samples used in the methods and assays of the present invention may be prepared by any available method or process.

Detection of splicing variants may be accomplished by amplifying specific fragments directly from a cDNA preparation from the tumor tissue using PCR. Presence of certain PCR product can be indicative of the presence of certain splicing variants, when the primers for the PCR are designed in such way that PCR products are only available when certain variants are present in the sample. Alternatively, primers may be designed to produce easily differentiable products for different variants. The sequence composition of the variants may also be determined from the amplified product.

The PCR reaction is well known in the art (See, e.g., U.S. Pat. No. 4,683,203; and U.S. Pat. No. 4,683,195). In general, the PCR procedure describes a method of gene amplification which is comprised of (i) sequence-specific hybridization of primers to specific genes within a DNA sample (or library), (ii) subsequent amplification involving multiple rounds of annealing, elongation, and denaturation using a DNA polymerase, and (iii) screening the PCR products for a band of the correct size. The primers used are oligonucleotides of sufficient length and appropriate sequence to provide initiation of polymerization, i.e. each primer is specifically designed to be complementary to each strand of the genomic locus to be amplified. The primers are prepared using any suitable method, such as conventional phosphotriester or phosphodiester methods or automated embodiments thereof (Beaucage, *Tet. Lett.* 22:1859-1862, 1981).

For the detection of splicing variants, primers may be designed to flank a certain exon that may be alternatively spliced, i.e., one primer is complementary to the 5' side of the exon, and the other primer is complementary to the 3' side of the exon. The PCR amplification products thus would show different sizes. When the exon is present, a larger amplification product is obtained. When the exon is absent, a smaller amplification product is obtained. Alternatively, a primer may be designed to be complementary to a nucleotide sequence within the exon. This way, PCR amplification product is only available when the exon is present in the specimen. Additionally, a primer may be designed to be partially complementary to the 3' end of an exon 5' to the

alternatively spliced exon, and partially complementary to the 5' end of an exon 3' to the alternatively spliced exon. PCR amplification product can only be obtained when the alternatively spliced exon is present in the sample.

5 The polymerization agent can be any compound or system (including enzymes) which will facilitate combination of the nucleotides in the proper manner to form the primer extension products which are complementary to each nucleic acid strand. Other fundamental conditions to allow amplification include the presence of nucleoside triphosphates and suitable temperature and pH (Thigpen et al., *J. Clin. Invest.* 90: 799-809, 1992; Saiki et al., *Science* 239: 487-491, 1988).

10 DNA sequences of the specified gene which have been amplified by use of polymerase chain reaction may also be screened using exon oligonucleotide probes. These probes are nucleic acid oligomers, each of which are complementary to a corresponding segment of the investigated gene and may or may not contain a known variant. The assay is performed by detecting the presence or absence of a hybridization signal for the specific sequence.

Oligonucleotide Probes

15 Another aspect of the subject invention is to provide for variant specific nucleic acid hybridization probes capable of detecting splicing variants of genes which predispose an individual to prostate cancer. The hybridization probes of the subject invention may be derived from the disclosed nucleotide sequences of the identified variants and form stable hybrids with the target sequences, under stringent to moderately stringent hybridization and wash conditions. Stringent conditions will be used in the case of perfect complementation with the target sequence, less stringent hybridization conditions will be used if mismatches are expected among the variants. Conditions will always be chosen such that nonspecific/adventitious bindings are eliminated or minimized. The probes may be of any suitable length, which span all or a portion of the specified gene region, and which allow specific hybridization.

20 Nucleic acid hybridization simply involves contacting a probe and target nucleic acid (from a nucleic acid sample) under conditions where the probe and its complementary target can form stable hybrid duplexes through complementary base pairing (see U.S. Pat. No. 6,333,155). Methods of nucleic acid hybridization are well known in the art. In a preferred embodiment, the probes are immobilized on solid supports such as beads, microarrays, or gene chips.

25 The probes include an isolated polynucleotide, preferably attached to a label or reporter molecule, may be used to isolate other polynucleotide sequences, having sequence similarity by standard methods. Techniques for preparing and labeling probes are known in the art and disclosed in Sambrook et al. (*Molecular Cloning: A Laboratory Manual*, Ed. 2; Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1989) or Ausubel et al. (*Current Protocols in Molecular Biology*, Wiley & Sons, New York, N.Y., 1995). The labels may be incorporated by any of a number of means well known to those of skill in the art (see U.S. Pat. No. 6,333,155). Commonly employed labels include, but are not limited to, biotin, fluorescent molecules, radioactive molecules, chromogenic substrates, chemiluminescent labels, enzymes, and the like. The methods for biotinylation of nucleic acids are well known in the art, as are methods for introducing fluorescent molecules and radioactive molecules into oligonucleotides and nucleotides.

30 Other similar polynucleotides may be selected by using homologous polynucleotides. Alternatively, polynucleotides encoding these or similar polypeptides may be synthesized or selected by use of the redundancy in the genetic code. 35 Various codon substitutions may be introduced, e.g., by silent changes (thereby producing various restriction sites) or to optimize expression for a particular system. Mutations

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may be introduced to modify the properties of the polypeptide, perhaps to change ligand-binding affinities, interchain affinities, or the polypeptide degradation or turnover rate.

Probes comprising synthetic oligonucleotides or other polynucleotides of the present invention may be derived from naturally occurring or recombinant single- or double-stranded polynucleotides, or be chemically synthesized. Probes may also be labeled by nick translation, Klenow fill-in reaction, or other methods known in the art.

Other means for producing specific hybridization probes for nucleic acids include the cloning of nucleic acid sequences into vectors for the production of mRNA probes. Such vectors are known in the art and are commercially available and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerase as T7 or SP6 RNA polymerase and the appropriate radioactively labeled nucleotides.

The nucleotide sequences may be used to construct hybridization probes for mapping their respective genomic sequences. The nucleotide sequence provided herein may be mapped to a chromosome or specific regions of a chromosome using well known genetic and/or chromosomal mapping techniques. These techniques include *in situ* hybridization, linkage analysis against known chromosomal markers, hybridization screening with libraries or flow-sorted chromosomal preparations specific to known chromosomes, and the like (Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York N.Y., 1988).

To detect the presence of the splicing variants of genes predisposing an individual to prostate cancer, a test sample is prepared and analyzed for the presence or absence of such susceptibility alleles. Thus, the present invention provides methods to identify the expression of one of the nucleic acids of the present invention, or homolog thereof, in a test sample, using a nucleic acid probe or antibodies of the present invention. In particular, such methods comprise incubating a test sample with one or more of oligonucleotide probes of the present invention (as described above) and assaying for binding of the nucleic acid probes or antibodies to components within the test sample.

Conditions for incubating a nucleic acid probe or antibody with a test sample depend on the format employed in the assay, the detection methods used, and the type and nature of the probe used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization or amplification formats can readily be adapted to employ the nucleic acid probes or antibodies of the present invention. Examples of such assays can be found in Chard, An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, Netherlands, 1986; Bullock et al., Techniques in Immunocytochemistry, Academic Press, Orlando, Fla. Vol. 1, 1982, Vol. 2, 1983, Vol. 3, 1985; Tijssen, Practice and Theory of Immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, Netherlands, 1985.

The test samples of the present invention include cells, protein or membrane extracts of cells, or biological fluids

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such as sputum, blood, serum, plasma, or urine. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing DNA extracts from any of the above samples are well known in the art and can be readily be adapted in order to obtain a sample which is compatible with the system utilized.

Gene Silencing

The phrase "gene silencing" refers to a process by which the expression of a specific gene product is lessened or attenuated. It is also used interchangeably with the term "gene knockdown." Gene silencing can take place by a variety of pathways. Unless specified otherwise, as used herein, gene silencing refers to decreases in gene product expression that results from RNA interference (RNAi), a defined, though partially characterized pathway whereby small inhibitory RNA (siRNA) act in concert with host proteins (e.g. the RNA induced silencing complex, RISC) to degrade messenger RNA (mRNA) in a sequence-dependent fashion. The level of gene silencing can be measured by a variety of means, including, but not limited to, measurement of transcript levels by Northern Blot Analysis, B-DNA techniques, transcription-sensitive reporter constructs, expression profiling (e.g. DNA chips), and related technologies. Alternatively, the level of silencing can be measured by assessing the level of the protein encoded by a specific gene. This can be accomplished by performing a number of studies including Western Analysis, measuring the levels of expression of a reporter protein that has e.g. fluorescent properties (e.g. GFP) or enzymatic activity (e.g. alkaline phosphatases), or several other procedures.

The term "siRNA" refers to small inhibitory RNA duplexes that induce the RNA interference (RNAi) pathway. These molecules can vary in length (generally between 18-30 basepairs) and contain varying degrees of complementation to their target mRNA in the antisense strand. Some, but not all, siRNAs have unpaired overhanging bases on the 5' or 3' end of the sense strand and/or the antisense strand. The term "siRNA" includes duplexes of two separate strands, as well as single strands that can form hairpin structures comprising a duplex region. Designing a siRNA molecule that can specifically silence a certain gene is well known in the art, and can be routinely carried out using methods similar to what is disclosed in U.S. Pat. No. 8,008,474, which is incorporated herein by reference. siRNA can be routinely introduced to cells through conventional means such as transfection.

For targeted silencing of certain splicing variant, siRNA can be designed to target a specific exon that is only present in one variant. The mRNA of the variant that include this exon will be selectively silenced. Alternatively, siRNA can be designed to target a specific exon junction, which will only exist when certain splicing event occurs. In other words, siRNA can be designed to target the junction sequence of an exon immediately 5' to the alternatively spliced exon and an exon that is immediately 3' to the alternatively spliced exon. This particular junction sequence would only exist in a continuous polynucleotide sequence within an mRNA when the alternatively spliced exon is lacking.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 87

<210> SEQ ID NO 1
<211> LENGTH: 3135
<212> TYPE: DNA

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

atgccccctg	gggtggactg	cccatggaa	ttctggacca	aggaggagaa	tcagagcg	60
gtgggttact	tcctgtgcc	cacagggtc	tacctgaact	tccctgtgc	ccgcaatg	120
aacctcagca	ccatcaagca	gctgctgtgg	caccgcgccc	agtatgagcc	gtcttcac	180
atgctcagtg	gccccgag	ctatgtgttc	acctgcata	accagacgc	ggageagcaa	240
gagctggagg	acgagcaac	gctgtgtgt	gacgtgc	gac	ccttctg	300
ctgggtggcc	gtgaggcg	ccgcgtgaag	aagctcatca	actcacagat	cagcctc	360
atcggcaaag	gcctccac	gtt	gactcc	ttgtgc	gacc	420
gccaagatgt	gccaattctg	cgaggaggcg	gcccggcg	ggcagcag	gt	480
gcctggctgc	agtacagttt	ccccctgc	ctggagcc	cg	gctcaaa	540
ggtaccctgc	ggctcccgaa	ccggggc	ctggtaac	ttaagtt	gag	600
gagagctca	ccttccagg	gtccacca	gacgtgc	tggcgt	gat	660
ctgcggaa	aggccac	gttccgg	ccgcgtgt	agcagccg	agactaca	720
ctgcagg	tgactac	tg	gatgc	accgc	cttcc	780
tacatctgca	gctgc	cagtgg	acc	ccatgt	ccat	840
tccatctcg	ccatgc	gg	tgac	gag	ccc	900
gccaaccac	ctccattcc	tgcaaga	c	ttcc	ctgt	960
cagccgttcc	gcatcg	catccagg	agca	cc	ccgt	1020
ctgggtgtc	aggccgg	tttccac	aac	gagat	tg	1080
tcggagg	gtgtgt	ggaggcc	tg	gaag	gt	1140
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<210> SEQ ID NO 3
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splice variants

<400> SEQUENCE: 3

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<400> SEQUENCE: 4

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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19
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<210> SEQ ID NO 9
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 9
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19
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<210> SEQ ID NO 10
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<220> FEATURE:
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 12

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<210> SEQ ID NO 13
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 13

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<210> SEQ ID NO 14
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<213> ORGANISM: Homo sapiens

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<210> SEQ ID NO 16
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<213> ORGANISM: Homo sapiens

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<210> SEQ ID NO 21
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<213> ORGANISM: Artificial Sequence
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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 33

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<210> SEQ ID NO 34
<211> LENGTH: 5301
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

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accgcggaaa tactgagaga actgagcatg gaatgtggcc tcaacaatcg catccggatg 180

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<210> SEQ ID NO 35
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 35

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<210> SEQ ID NO 36
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 36

ugggcugaa agcugcuuc 19

<210> SEQ ID NO 37
<211> LENGTH: 1830
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

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105**106**

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<210> SEQ ID NO 38
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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

 <400> SEQUENCE: 38

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<210> SEQ ID NO 39
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

 <400> SEQUENCE: 39

ccaccatctt ctcgtgtgc t 21

<210> SEQ ID NO 40
 <211> LENGTH: 19
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

 <400> SEQUENCE: 40

guggagcaca ucgagaaga 19

<210> SEQ ID NO 41
 <211> LENGTH: 19
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

 <400> SEQUENCE: 41

ucuucucgau gugcuccac 19

<210> SEQ ID NO 42
 <211> LENGTH: 19

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 42

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<210> SEQ ID NO 43
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 43

uucuuuccugu gagaugugg                                19

<210> SEQ ID NO 44
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 44

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<210> SEQ ID NO 45
<211> LENGTH: 1707
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

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<210> SEQ ID NO 46
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 46

ccucgucugu guuuccggaa 19

<210> SEQ ID NO 47
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 47

uuccggaaaca cagacgagg 19

<210> SEQ ID NO 48
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 48

gatgggtggag ggatggctgc 20

<210> SEQ ID NO 49
<211> LENGTH: 1714
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

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<210> SEQ ID NO 50
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 50

gguggaggga uggcugcau 19

<210> SEQ ID NO 51
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 51

augcagccau cccuccacc 19

<210> SEQ ID NO 52
<211> LENGTH: 3099
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 53

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<210> SEQ ID NO 54
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 54

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<210> SEQ ID NO 55
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 55

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<210> SEQ ID NO 56
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 56

ucaaugucuu cauacuccc 19

<210> SEQ ID NO 57
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 57

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21

<210> SEQ ID NO 58
<211> LENGTH: 2948
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

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<210> SEQ ID NO 59
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 59

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<210> SEQ ID NO 60
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 60

ԱԱԾԱՆԱԳԸԱՆ ԸՆԿԱՆԱԿԱՆ 19

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<210> SEQ ID NO 61
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 61

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<210> SEQ ID NO 62
<211> LENGTH: 4226
<212> TYPE: DNA
<213> ORGANISM: *Homo sapiens*

<400> SEQUENCE: 62

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ttgctgagta caagactggg cctgtgctgg aacacccaga ttgttccca tgtcaggact	300
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<210> SEQ ID NO 63
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 63
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19

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<210> SEQ ID NO 64
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 64

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<211> LENGTH: 4651	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 65	
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21

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19

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19

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19

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19

151**152**

What is claimed is:

1. An siRNA molecule characterized by a length of 15 to 31 nucleotides and that inhibits expression of PIK3CD and/or splicing variants thereof comprising:
 - a) a duplex region comprising a sense region and an antisense region, wherein the sense and antisense regions of the duplex region each consist of 15-31 nucleotides and wherein the sense region includes a PIK3CD variant splice junction and is homologous with at least 15 nucleotides of SEQ ID No. 12; and
 - b) an overhang region of 0-6 nucleotides.
2. The siRNA molecule of claim 1, wherein the antisense region is complementary to SEQ ID No. 12.
3. The siRNA molecule of claim 1, wherein the overhang region is 2 nucleotides in length.
4. The siRNA molecule of claim 1, wherein the siRNA molecule has no overhang region.
5. The siRNA molecule of claim 1, wherein the siRNA molecule is chemically synthesized.
6. An siRNA molecule that inhibits expression of PIK3CD and/or splicing variants of, wherein the siRNA is characterized by a length of 15 to 31 nucleotides, includes a PIK3CD variant splice junction, and is homologous with at least 15 nucleotides of SEQ ID No. 12.
7. The siRNA molecule of claim 6, comprises an overhang region of 0-6 nucleotides.
8. The siRNA molecule of claim 6 wherein the siRNA molecule is a single stranded molecule that can form hairpin structures comprising a duplex region.

* * * * *

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